

REVIEW AND EVALUATION OF CLINICAL DATA

DEC 8 1998

Application Information

NDA 20-919

Sponsor: Pfizer Inc.

User Fee Due Date: December 17, 1998

Drug Name

Generic Name: Ziprasidone Mesylate

Trade Name: Zeldox IM

Drug Characterization

Pharmacologic Category: Serotonin and Dopamine Antagonist

Proposed Indication: Acute Control and short-term management of the
agitated psychotic patient

NDA Classification: 3S

Dosage Forms: IM for injection; 20 mg ziprasidone/mL

Reviewer Information

Clinical Reviewer: Roberta L. Glass, M.D.

Review Completion Date: November 13, 1998

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1.0 Material Utilized in Review

1.1 Material from NDA/IND

This NDA submission was presented in a combination of hard copy and electronic format. Case report forms were submitted in electronic format only. There were no electronic data sets provided for this review.

The documents most frequently referred to for the purposes of this review were the following:

Integrated summary of efficacy
Integrated summary of safety
Study reports for trials 125 and 126
Literature summary

Also considered were Pfizer's commercial INI _____ NDA 20-825 (ziprasidone po for psychotic disorders) and IND _____

Case report forms were examined for the following subjects: 125-795-0071 and 126-063-80121.

1.2 Related Reviews, Consults, etc.

The Division of Cardio-Renal Drug Products was consulted for issues concerning ziprasidone's cardiovascular adverse events, review by Sugbok K. Chun, M.D. (HFD-110:10/23/98), and by Charles J. Ganley, M.D. (HFD-110: 11/18/98 and 1/6/98). Also referred to were the following documents: 1) Clinical Pharmacology and Biopharmaceutics Review by Sayed Al-Habet, Ph.D. (HFD-860: 5/22/98), 2) Statistical Review and Evaluation by Sue-Jane Wang, Ph.D. (HFD 710 & 715), 3) Summary and Evaluation of Pharmacology and Toxicology by Lois M. Freed, Ph.D. (HFD:120: draft), 4) CDER correspondence of nonapprovable letter to Pfizer for NDA 20-825 by Robert Temple, M.D. (HFD-101: 6/17/98) 5) Memorandum Re: Pfizer NDA 20-825 by Paul Leber, M.D. (HFD-120: 6/1/98), 6) Memorandum Re: Pfizer NDA 20-825 by Thomas P. Laughren, M.D. (HFD-120: 5/14/98), and 7) Review and Evaluation of Clinical Data of Ziprasidone HCL:NDA 20-825 by Roberta L. Glass, M.D. (HFD-120: 4/30/98).

1.3 Other Resources

Dr. Andrew Mosholder provided excellent mentoring during the review process.

2.0 Background

2.1 Indication

Of the currently nine antipsychotic medications available in the intramuscular form for the indication of acute agitation, all are considered to be traditional dopamine antagonist agents. There have been few efforts of drug development for an intramuscular formulation of the more recently marketed 'atypical' antipsychotic agents (i.e. antipsychotics possessing both serotonin type 2 and dopamine receptor antagonist properties). It has been suggested that these 'atypical' agents may reduce the incidence of EPS, result in less risk of the development of tardive dyskinesia, and may be more effective in treating the negative symptoms of schizophrenia.

2.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents

Pfizer submitted NDA 20-825 for the oral formulation of ziprasidone HCl with the indication for the treatment of psychotic disorders in March, 1997. A nonapprovable letter was sent to Pfizer for NDA 20-825 on June 17, 1998 indicating that ziprasidone's ability to prolong the QTc interval presented a risk of potentially fatal ventricular arrhythmias which did not outweigh the benefits of ziprasidone compared to

already marketed antipsychotics. Also of note was the high sudden death rate observed within the NDA data base.

This current NDA 20-919 for the intramuscular formulation of ziprasidone was submitted on December 18, 1997. The proposed labeling incorporates the previously submitted labeling of the oral formulation which was not approved.

This sponsor also has the active IND _____ to study oral ziprasidone.

According to a teleconference of July 21, 1998 with Dr. Ritrovato from Pfizer, all clinical studies of ziprasidone have been done under Pfizer's sponsorship.

2.3 Administrative History

The original commercial IND for intramuscular ziprasidone was filed on October 30, 1995. It was determined, based on human pharmacokinetic data, that the IM and PO formulation of ziprasidone were not bioequivalent. DNDP sent a letter to the sponsor in March, 1996 suggesting approaches to establish efficacy such as focusing on the indication of agitation and restlessness in acutely psychotic patients. DNDP sent a letter (7/10/96) to the sponsor regarding the lack of placebo control in study 128-125, which was proposed to be a pivotal study, and the need to show a between group difference or a dose response relationship; it was also suggested that the sponsor consider adding an active control group such as lorazepam. In a facsimile of December 19, 1996, Dr. David Hoberman, FDA statistician, communicated that no correction for multiple comparisons for the two pivotal studies (125 & 126) was acceptable if the randomization lists were completely separate, and if investigators were not identical between the two studies.

A pre-NDA meeting was held on August 13, 1997, during which the sponsor discussed their concerns regarding labeling for the indication of short-term management of agitated psychotic patients. Approaches of presenting efficacy and safety data were also discussed.

In a facsimile of August 25, 1997, Dr. Lois Freed, pharmacologist, recommended that the sponsor conduct one month rat and dog studies using the IM excipient, sulphobutylether beta-cyclodextrin (SBECD) rather than only the intravenous formulation; in addition, it was recommended that the NDA include multiple dose toxicokinetic data for IM ziprasidone.

During a meeting on August 14, 1997, FDA chemistry reviewers and the sponsor discussed that NDA stability data would be required for the excipient, SBECD, because it has not been previously available commercially.

2.4 Proposed Labeling

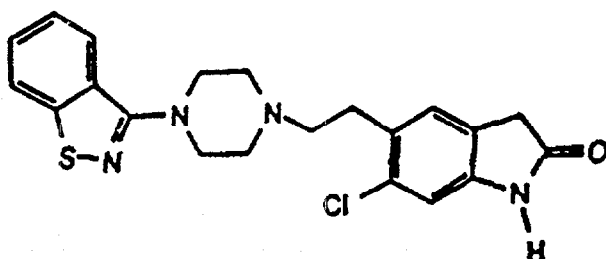
The dosing instructions in the draft labeling recommend an initial dose of 10 to 20 mg, with subsequent doses of 10 mg to be administered every 2 hours, or 20 mg to be administered every 4 hours. The labeling states that the recommended maximum dosage is 80 mg/day, and that use for more than 3 consecutive days has not been studied.

2.5 Foreign Marketing

According to a teleconference of 7/21/98 with Dr. Charles Ritrovato from Pfizer, ziprasidone is not marketed anywhere in the world.

3.0 Chemistry

The chemical structure for the free base of ziprasidone is:



The chemical structure for the vehicle, beta-cyclodextrin sulfobutyl ether sodium (SBECD) is:

4.0 Animal Pharmacology and Toxicology

Renal tubule epithelial vacuolation was observed in animal toxicology studies using the intravenous formulation of Sulphobutylether Beta-Cyclodextrin (SBECD); the sponsor states that these changes were reversible following cessation of treatment. There were also dose related incidence and severity of foamy macrophages in the liver and lungs.

Similar renal tubular vacuolation was observed in animal studies of the intravenous formulation of ziprasidone. Also increased heart rates was observed in a 2 week dog study. Rabbit studies provided evidence for discomfort at the site of injection of ziprasidone tartrate, but not with ziprasidone mesylate.

5.0 Description of Clinical Data Sources

5.1 Primary Source Data (Development Program)

Appendix 5.1.1.1 lists the cumulative number of subjects in the integrated safety data base. The cut-off date for the safety information was July 31, 1997. The integrated safety data base includes the Phase I study 046 which studies patients with the diagnosis of schizophrenia, schizoaffective or schizotypal personality disorder (not with an acute exacerbation for at least 6 months prior to participation). There were a total of 523 subjects in the integrated safety data base.

Please refer to Appendix 5.1.1.2 for a listing of all studies. The integrated safety data base includes one Phase I study (046), 5 Phase II/III (121, 125, 126, 306, 120), and two extension studies (127E and 306E).

The safety data submitted also includes 4 clinical studies testing the excipient Sulphobutylether Beta-Cyclodextrin (SBECD) which are not integrated in the safety data base for ziprasidone IM. The number of healthy subjects exposed to the excipient is 48. There are no subjects days exposure calculated. Please see Appendix 5.1.1.3 for listing of all Phase I studies utilizing the excipient SBECD.

5.1.1 Study Type and Design/Patient Enumeration

5.1.2 Demographics

Please refer to Appendix 5.1.2.1 for a demographic profile of all Phase I studies.

Appendix 5.1.2.2 contains the demographic profile for the Phase I studies for SBECD.

The demographic profile for subjects in the integrated safety data base (including Phase I study 046 and all Phase II/III studies) is listed in Appendix 5.1.2.3. For clarification of the sponsor's categorization, "other ziprasidone" refers to all ziprasidone treatment groups except the ziprasidone 2mg group; "combined ziprasidone" refers to all ziprasidone treatment groups including the ziprasidone 2mg groups.

The majority of subjects included in the integrated safety data base are Caucasian males 19 to 76 years old.

5.1.3 Extent of Exposure (dose/duration)

The modal daily dose and duration for Phase I studies for ziprasidone IM are shown in Appendix 5.1.3.1. All subjects were exposed to a low daily dose (≤ 20 mg ziprasidone IM). Appendix 5.1.3.2 summarizes the available information regarding modal daily dose of SBECD in phase I studies.

The modal daily dose for Phase II/III studies (also including phase I study 046) are shown in Appendix 5.1.3.3. This table shows that the majority of subjects were exposed to doses between 5 to 40 mg ziprasidone IM daily for a mean duration of 2 days. There have been 369 subjects (70.6 %) within this pool who were exposed to daily doses ranging from 5-60 mg ziprasidone IM; 69 subjects (13.2%) were exposed to daily doses > 60 mg, and 85 subjects (16.3%) exposed to daily doses < 5 mg. The mean exposure time was 2 days while 245 subjects (46.8%) were exposed to ziprasidone IM for 3 days. The proposed labeling recommends that the initial dose be 10-20 mg and the maximum daily dose be 80 mg ziprasidone IM, and that treatment beyond 3 days was not studied.

The following table summarizes the person time in the ziprasidone IM safety data base:

Subject-years exposure in ziprasidone safety data base*

ORIGINAL NDA	ZIPRASIDONE	HALOPERIDOL	PLACEBO
N=	523	142	6
Subject-days exposure*	1144	371	18

Includes phase I study 046 which included subjects with diagnosis of schizophrenia, schizoaffective or schizotypal personality disorder, but did not have acute exacerbation for at least 6 months.

Appendix 5.1.3.2 summarized the exposure of IV SBECD in Phase I studies.

5.2 Secondary Source Data

5.2.1 Other Studies

There were no other studies conducted.

5.2.2 Postmarketing Experience

As of July 21, 1998, ziprasidone IM is not marketed in any country as per a teleconference with Dr. Ritrovato at Pfizer.

5.2.3 Literature

According to a teleconference of July 21, 1998 with Dr. Ritrovato from Pfizer, all clinical studies have been done under Pfizer's sponsorship and are included in the current NDA submission.

The Sponsor included approximately 100 published papers and abstracts (NDA Vol. 54-57) that contained some information regarding ziprasidone. The literature search encompassed the years of 1966 through 1996. The literature search was conducted by David Larson, Ph.D. who has been employed by Pfizer since 1971.

A review of the sponsor's literature search did not reveal any unexpected safety findings.

6.0 Human Pharmacokinetic Considerations

For complete details, please refer to the biopharmaceutics review.

Ziprasidone mesylate IM demonstrated an absolute bioavailability of 100%. Single IM doses to healthy male subjects revealed a terminal half-life of approximately 2.9 hours (ranging 2.1 to 3.8 hours). After multiple dose administration in schizophrenic subjects for three days, the terminal half-life ranged from 6.7 to 13.4 hours, suggesting that half life was longer after multiple dosing.

The maximum concentration was achieved in approximately 0.6 hours after injection (ranging from 0.17 to 1.5 hours). Systemic clearance after a single IM dose of 5-20 mg in healthy volunteers was 4.9 ml/min/kg (ranging 4-6 ml/min/kg). In the range of 5-40 mg, the AUC and Cmax were observed to increase in a dose related manner.

There were no metabolites identified for ziprasidone mesylate IM. For oral ziprasidone HCl, the major metabolites were ziprasidone-sulfoxide and ziprasidone-sulfone; both demonstrated a low affinity to D₂ and 5HT_{2A} receptors. For oral ziprasidone, in vitro studies of human liver microsomes suggest that ziprasidone is a cytochrome P450 3A4 substrate mainly for the metabolic processes of sulfur oxidation and N-dealkylation.

Also of note is that ziprasidone mesylate IM was not tested on patients with hepatic or renal impairment. This becomes a note of concern since the cyclodextrin excipient is cleared by renal filtration. The sponsor included a mention of this precaution under the special populations section.

7.0 Review of Efficacy

7.1 Background

Pfizer reports that they have two well controlled studies testing the effectiveness of ziprasidone in treating acute agitation in subjects who have psychotic disorders. In lieu of a placebo control, the sponsor used a low dose (2 mg ziprasidone IM) control group making comparisons with a higher dose ziprasidone group to support claims of efficacy. This review will discuss the following studies which were randomized, double blind, fixed dose, flexible schedule, multicentered trials in subjects diagnosed with psychotic disorders:

Study 125, n=117 total, comparing 2 mg ziprasidone IM and 10 mg ziprasidone IM in a flexible dose schedule with a maximum of 4 doses in the 24 hour study period.

Study 126, n=79 total, comparing 2 mg ziprasidone IM and 20 mg ziprasidone IM in a flexible dose schedule with a maximum of 4 doses in the 24 hour study period.

7.2 Review of individual studies

7.2.1 Study 125

Investigators/Location

This study was conducted in 17 centers in the United States. Please refer to Appendix 7.2.1.1 for the sponsor's list of investigators and sites. Ten additional sites (585, 599, 663, 697, 707, 767, 774, 786, 784, 785) were terminated prior to randomization of any subjects; the sponsor did not provide reasons for closing these sites.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to evaluate the safety and efficacy of ziprasidone IM in treating subjects with a psychotic disorder and acute agitation.

Population

Subjects chosen for this study were physically healthy males and females aged 18 years and older with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, schizophreniform disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder or psychotic disorder, NOS. Females of childbearing potential were required to use medically accepted forms of contraception during the study. Baseline scores (obtained within 4 hours of first double blind dose administration) were required to be ≥ 3 (mild) in at least three of the following items of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS): anxiety, tension, hostility, and excitement. The protocol allowed investigator discretion for a positive benzodiazepine or cannabinoids result in the urine drug screen; otherwise, it was required to be negative. Excluded from this study were patients with bipolar disorder without psychotic features, mental retardation, substance-induced psychotic disorder, psychoactive substance abuse/dependence within the preceding 2 months of the study, history of alcohol abuse, use of clozapine within 12 weeks prior to screening, and a high risk for suicide or homicide. Concurrent medications allowed during the double-blind trial period included benztropine (prn EPS), propranolol (prn EPS), lorazepam (prn agitation or insomnia) and temazepam (prn insomnia). Also allowed was chronic use (at least 2 months prior to study) of antihypertensives, diuretics, oral hypoglycemics, and hormone replacements (not insulin). Medications which required clearance from the sponsor's clinical monitor included psychotropic drugs (other than allowed as above), anorexics, antianginal agents, antiarrhythmics, antihistamines (terfenadine, astemizole), anticoagulants, steroids, theophylline, tryptophan, diuretics, H₂ blockers, cisapride, anti-infectives and all over the counter medications. Use of antiemetics was prohibited.

Design

This was a randomized, double-blind inpatient trial comparing two dose regimens of ziprasidone (2 mg vs. 10 mg ziprasidone IM). Screening included ECG, CBC, urinalysis, routine labs, urine drug screen, beta-HCG (for women), hepatitis battery, and lithium levels. ECGs and physical exams were repeated at baseline and at study endpoint (at least six hours after last dose); CBC, urinalysis and routine labs were repeated at study endpoint only. Vital signs were to be monitored at screening, just prior to dosing and 30 and 60 minutes post dosing. Serum samples to determine pharmacokinetic properties would be collected at study endpoint only. Baseline data was to be collected within four hours prior to administration of the first dose of double blind medication. Baseline assessments included the Behavioural Assessment Scale (BAS), Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), Nurses Observation Scale for Inpatient Evaluation (NOSIE), Simpson-Angus Rating Scale (SARS), Barnes Akathisia Scale, AIMS and ECG. Each patient's chart was to be reviewed to assess appropriateness for the study. After subjects were randomly assigned to either the 2 mg ziprasidone IM group or the 10 mg IM group, they would receive an initial dose with

successive doses administered at least 2 hours apart. In the 24 hour period of the study, patients could receive a maximum of four doses (8 mg ziprasidone IM for the 2mg group, and 40 mg ziprasidone IM for the 10 mg group). Investigators could choose to halt or administer less frequent treatments when a patient's agitation appeared to resolve.

The Behavioural Assessment Scale (BAS) was to be measured at the following times: 1) screening, 2) just prior to dose administration, 3) 15, 30, 45, 60, 90 minutes, and 2 hours after dose administration, and then hourly until either the next IM dose or termination. The CGI-S, CGI-I, NOSIE, SARS, and Barnes Akathisia Scale were to be administered at screening, baseline (up to 4 hours prior to dose administration), 4 hours after the first dose and at study endpoint. Study endpoint is defined as: 1) the longer of either 6 hours after last dose or at the end of the 24 hour period, or 2) the time of early termination.

Analysis Plan

There were three primary efficacy variables defined in the protocol: 1) the area under the curve (AUC) for measurements of the Behavioural Assessment Scale (BAS) from 0 to 2 hours after the first dose, 2) changes from baseline to 4 hours of the CGI-S score, and 3) changes from baseline to study endpoint of the CGI-S. The protocol states that linear models were to be used for analysis of the AUC with log transformations if required by data distribution. Linear models would also be used to analyze the CGI-S, but in case of violations of linear model assumptions, methods of categorical data analysis were to be utilized. Rank transformation may be used for change from baseline scores if required by the data distribution. Interaction effects of center and treatment were also to be analyzed.

In order to detect a difference of 1 point in the mean change from baseline of the CGI-S between the two treatment groups, the sponsor estimated a sample size of 50 subjects per group to provide 80 % power ($\alpha=0.05$, two tailed).

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 143 patients screened to enter the study, 117 patients were randomized to one of the two treatment group and received at least one IM injection. Reasons for not being chosen to participate in this trial were not provided in this submission.

The following table from the sponsor's study report itemizes reasons for discontinuation from the two treatment groups:

Discontinuations from Study Ziprasidone Protocol 125		
Number (%) of Subjects	Ziprasidone 2mg 54	Ziprasidone 10mg 63
Discontinuations		
Related to Study Drug	1 (1.9)	2 (3.2)
Adverse event	1 (1.9)	2 (3.2)
Not Related to Study Drug	1 (1.9)	0
Protocol violation	1 (1.9)	0
Total	2 (3.8)	2 (3.2)

The dropout rates for the treatment group taking ziprasidone 10 mg IM and the group taking 2 mg IM were almost identical at less than 4%.

Appendix 7.2.1.2 displays the number of subjects who received one, two, three or four injections within the 24 hour period of the study. Within the twenty-four hour period, one injection was used to treat 24.1% (13 of 54) of the 2mg IM group, while 36.5% (23 of 63) of the 10mg IM group received only one injection. The

rates of subjects receiving two and three injections were similar for both groups. Four injections (the maximum allowed) were administered to 24.1% (13 of 54) in the 2 mg IM group and 14.3% (9 of 63) in the 10 mg IM group.

Demographics /Group Comparability

The majority of patients in this study were Caucasian males with the mean age of approximately 40 years old. The mean age of the female patients was similar to the males. There did not appear to be imbalances in the treatment groups. Appendix 7.2.1.3 shows the breakdown of demographics by treatment group.

The mean baseline values for the CGI-S and the BAS (see below) were slightly lower in the 2 mg ziprasidone IM group but are comparable to the 10 mg ziprasidone IM group. The sponsor did not provide any statistical comparisons of the baseline values.

Mean Baseline Values of Primary Efficacy Variables -Study 125

MEAN SCORE	ZIPRASIDONE IM 2 MG GROUP	ZIPRASIDONE IM 10 MG GROUP
CGI-S	4.24	4.37
BAS	4.65	4.81

Concomitant Medications

In both groups, lorazepam was used by approximately 10% of the patients during the study. Please refer to the following table for select concomitant medication use:

Selected concomitant medication used in Study 125

	Ziprasidone IM 2 mg (n=54)	Ziprasidone IM 10 mg (n=63)
Lorazepam	5	6
Temazepine	3	3
Benzotropine	8	6
Beta-Blocker	3	0
Antidepressant	0	1

Lorazepam was used by

Efficacy Results

Please refer to Appendix Tables for results of the primary outcome measures (CGI-S at 4 hours, CGI-S at endpoint, and AUC of BAS at 2 hours). When compared to the 2 mg ziprasidone IM group at a 95 % confidence interval, the 10 mg ziprasidone IM group demonstrated a statistically significant difference in the AUC of the BAS (0 to 2 hours). However, there was no statistical significance observed between the 2 and 10 mg ziprasidone IM groups when comparing mean changes from baseline of the CGI-S scores at 4 hours and at study endpoint. The sponsor also submitted an analysis of a subgroup of subjects with BAS scores ≥ 5 which had similar efficacy results to the total sample tested (please refer to Miscellaneous Issues for further discussion of BAS).

Miscellaneous Issues

This Behavioural Assessment Scale was developed by Pfizer to assess the effects of this IM medication. Because it is a new scale, there is no literature establishing it as a standardized rating scale. This BAS appears to be an instrument which combines two subscales—one assessing degree of agitation and one assessing levels of consciousness:

Behavioural Assessment Scale (BAS):

- 1 = difficult or unable to rouse;
- 2 = asleep, but responds normally to verbal or physical contact;
- 3 = drowsy, appears sedated;
- 4 = quiet and awake (normal level of activity);
- 5 = signs of overt activity (physical or verbal), calms down with instructions;
- 6 = extremely or continuously active, not requiring restraint;
- 7 = violent, requires restraint

There was no required baseline scoring of the BAS in the inclusion criteria. The mean BAS score presented by the sponsor was 4.65. According to the efficacy tables, it appears that approximated 70% (45 of 63 subjects) of the subjects had baseline scores of ≥ 5 while the remainder had BAS scores less than 5. It is questionable if a BAS score of 5 (indicating that a person is likely to respond to instruction) or lower is typical of patients for whom this IM medication would be indicated as IM medication is usually reserved for patients who are too agitated to follow directions to swallow a pill.

When viewing the psychiatric inclusion criteria further, it is noted that the baseline scores for the PANSS were required to be ≥ 3 (mild) in at least three of the following items of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS): anxiety, tension, hostility, and excitement as follows:

PANNS:

Anxiety: 3 (mild): Expresses some worry, over-concern, or subjective restlessness, but no somatic and behavioral consequences are reported or evidenced.

Tension: 3 (mild): posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of position, or fine rapid hand tremor.

Hostility: 3 (mild): Indirect or restrained communication of anger, such as sarcasm, disrespect, hostile expressions, and occasional irritability.

Excitement: 3 (mild) tends to be slightly agitated, hypervigilant, or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked mood lability. Speech may be slightly pressured.

Again, it is questionable if a patient whose profile fits a PANNS score of 3 (mild) in the above items would be representative of subjects who clinically requires an intramuscular injection of an antipsychotic as opposed to the less invasive treatment of oral medication.

Conclusions

Because this study demonstrated statistical significance in only one of the three primary efficacy variables, it merely provides fair evidence for the effectiveness of ziprasidone IM treating agitation in psychotic psychiatric patients.

7.2.2 Study 126

Investigators/Location

This study was conducted in 18 centers in the United States. Please refer to Appendix 7.2.1.2 for the sponsor's list of investigators and sites. Two additional sites (777 and 793) were terminated prior to randomization of any subjects; the sponsor did not provide reasons for closing these sites.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to evaluate the safety and efficacy of ziprasidone IM in treating subjects with a psychotic disorder and acute agitation.

Population

Please refer to Study 125 which had the same entrance criteria. Concurrent medications were similar to those used in Study 125.

Design

This was a randomized, double-blind inpatient trial comparing two dose regimens of ziprasidone (2 mg vs. 20 mg ziprasidone IM). The details of this study's design were similar to Study 125 (please refer to Study 125 for more information).

Once chosen for the study, subjects were to be randomized to one of two treatment groups: 1) 2 mg ziprasidone IM, or 2) 20 mg ziprasidone IM. After the initial dosing of 2 mg or 20 mg ziprasidone IM, repeat dosing was to have been administered at least 4 hours apart. The maximum allowed dose in the 24 hour period of the study was 8 mg for the 2 mg ziprasidone IM group, and 80 mg for the 20 mg ziprasidone IM group. Investigators could choose to halt or administer less frequent treatments when a patient's agitation appeared to resolve.

Assessment scales included a Behavioural Assessment Scale (BAS), PANSS, CGI, NOSIE, Simpson-Angus Scale, Barnes Akathisia Scale, and AIMS. The schedule of assessment was similar to Study 125 (Please see Study 125 for further details regarding the use of these instruments).

Analysis Plan

The primary efficacy variables were listed as: 1) the area under the curve (AUC) for the Behavioural Assessment Scale (BAS) from 0 to 4 hours after the first IM dose, 2) change from baseline to 4 hours of CGI-S score, and 3) change from baseline to study endpoint of the CGI-S. The protocol states that linear models including center and treatment were to be utilized for the analysis of the AUC with log transformations if required by data distribution. Linear models were also to be attempted to analyze the CGI-S, but in case of violations of linear model assumptions, methods of categorical data analysis were to be applied. Rank transformation would be used for change from baseline scores if required by the data distribution. Interaction effects of center and treatment were also to be analyzed.

In order to detect a difference of 1.5 points in the mean change from baseline of the CGI-S between the two treatment groups, the sponsor estimated a sample size of 30 subjects per group to provide 80 % power ($\alpha=0.05$, two tailed).

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 99 subjects screened to enter the study, 79 were randomized to one of the two treatment groups. Reasons for not being chosen to participate in this trial were not provided in this submission.

The following table from the sponsor's study report summarizes the discontinuation rate:

Discontinuations from Study Ziprasidone Protocol 126		
	Ziprasidone 2mg 38	Ziprasidone 20mg 41
Discontinuations		
Related to Study Drug	1	0
Lack of efficacy	1	0
Not Related to Study Drug	1	3
Adverse event	1	0
Subject defaulted	0	3
Total	2 (5.3%)	3 (7.3%)

The dropout rate for the treatment group taking ziprasidone 20 mg IM was slightly higher than for the group taking ziprasidone 2 mg IM, but by only one patient.

Appendix 7.2.2.2 displays the number of subjects who received one, two, three or four injections within the 24 hour period of the study. Within this twenty-four hour period, one injection was used to treat 26.3% (10 of 38 patients) of the 2mg IM group, while 41.5% (17 of 41) of the 20mg IM group received only one injection. For the administration of subsequent dosing (i.e. 2, 3 or 4 injections), the 20 mg IM group had a slightly lower rate than the 2mg IM ziprasidone group.

Demographics /Group Comparability

The majority of patients in this study were Caucasian males with the mean age of approximately 40 years old. The mean age of the female patients was similar to the males. There did not appear to be imbalances in the treatment groups. Appendix 7.2.2.3 shows the breakdown of demographics by treatment group.

The 2 mg ziprasidone IM group and the 10 mg ziprasidone IM group had comparable scores for the mean baseline values of the CGI-S and the BAS as can be seen in the following table:

Mean Baseline Values of Primary Efficacy Variables - Study 126

MEAN SCORE	ZIPRASIDONE IM 2 MG GROUP	ZIPRASIDONE IM 20 MG GROUP
CGI-S	4.74	4.63
BAS	5.00	4.98

Concomitant Medications

During the study, lorazepam was used at a higher rate in the ziprasidone 20 mg IM group (15%) than the ziprasidone 2 mg IM group (8%). Please refer to the following table for select concomitant medication use:

Selected concomitant medication used in Study 126

	Ziprasidone IM 2 mg (n=38)	Ziprasidone IM 20 mg (n=41)
Lorazepam	3	6
Temazepine	0	1
Benzotropine	3	3
Beta-Blocker	3	0
Antipsychotic	0	1

Efficacy Results

Please refer to Appendix Tables for results of the primary outcome. When compared to the 2 mg ziprasidone IM group at a 95 % confidence interval, the 20 mg ziprasidone IM group demonstrated a statistically significant difference in the AUC of the BAS (0 to 4 hours), the mean changes from baseline

of the CGI-S scores at 4 hours and at study endpoint.

Miscellaneous Issues

Please refer to Study 125 (Miscellaneous Issues) for a discussion about the BAS scale and the psychiatric entrance requirement.

Conclusions

This study demonstrated statistical significance in the three defined efficacy variables when comparing the 20 mg ziprasidone IM treatment group with the 2 mg ziprasidone IM treatment group. Therefore, these results provide evidence that ziprasidone IM is effective in treating agitation in psychotic psychiatric patients.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

When exploring how demographic characteristics may have affected the efficacy data, the sponsor claims to have found no significant effect on treatment based on age, gender, or race. The p-values are not significant for the interaction effects of age (<55 years or ≥ 55 years), gender, race (Caucasian or African American) and any of the efficacy variables tested (AUC of BAS 0-2 hours, AUC of BAS 0-4 hours, CGI-S).

7.3.2 Choice of dose

In study 126, ziprasidone IM was shown to be efficacious when comparing the higher dose treatment group (20 mg ziprasidone IM) to the lower dose treatment group (2 mg ziprasidone IM). However, in study 125, the higher dose treatment group (10 mg vs 2 mg ziprasidone IM) demonstrated a statistically significant difference in one of three primary efficacy variables. These results could provide support that the higher dose of ziprasidone 20 IM may demonstrate a better efficacy profile.

The sponsor has recommended that the initial intramuscular dose of ziprasidone be 10 to 20 mg. It further states that subsequent doses of 10 mg may be administered as often as every 2 hours, or 20 mg every 4 hours as needed with a maximum recommended daily dose of 80 mg. This information accurately reflects the findings from these efficacy studies.

7.3.3. Duration of Treatment

A greater percent of patients in the higher dose treatment groups, compared to the low dose ziprasidone 2mg IM group, were administered only one injection in the 24 hour studies in both studies 125 and 126. It appears that the higher dose group (20 mg ziprasidone IM) in study 126 had a slightly higher percent of subjects receiving only one injection than the higher dose group in study 125 (10 mg ziprasidone IM). After the first injection, all treatment groups in both studies had comparable rates of subsequent injections.

As stated above, the proposed labeling offers a dosing schedule with 80 mg ziprasidone as the maximum recommended daily dosing. The labeling further states that use of ziprasidone IM greater than 3 days has not been tested. These recommendations reflect the guidelines used in the clinical trials of ziprasidone IM.

7.4 Conclusions regarding efficacy data

Ziprasidone IM has been clearly proven to be effective in the treatment of agitation in psychotic patients in one well controlled study which compared the dose of 20 mg ziprasidone IM to a low dose (2 mg) ziprasidone IM. Results of a second well controlled trial comparing the dose of 10 mg ziprasidone IM with a low dose (2mg) ziprasidone control group provided some support for the efficacy of ziprasidone IM at this dose.

Because of the sedative properties of ziprasidone IM, it may not be surprising that patients appear less psychotic in the 20 mg ziprasidone IM group of study 126 (i.e. significant improvement of CGI scores compared to the low dose group) than the 10 mg ziprasidone IM group of study 125. If effectiveness for an IM treatment of agitation is best reflected by the parameter of AUC of the BAS, then the presented data has proven ziprasidone to be efficacious in the treatment of acute agitation in patients who have psychotic disorders.

8.0 Integrated Review of Safety

8.1 Methods and Findings for Safety Review

The sponsor submitted the integrated safety data base for all Phase II/III studies for review. This data base also included one Phase I study (046) which included subjects diagnosed with a psychotic disorder. The main focus of the safety review was on the integrated safety data base to identify significant adverse events. Cardiovascular safety issues were explored in depth by cardiology consultant, Dr. Chun (HFD-110), who reviewed three Phase I studies (033, 038, 046) and one Phase III study (121).

The determination of common adverse events presented some difficulty in this review as there were no placebo controlled studies. As a substitute for placebo controlled studies, the sponsor submitted two well controlled studies (125 and 126) which used a low dose (2 mg/dose; maximum qid) ziprasidone IM group as a control group to be compared to a higher dose ziprasidone group. The higher dose group for study 125 was 10 mg ziprasidone IM group (maximum qid), and study 126 used a 20 mg ziprasidone IM group (maximum qid) to compare with the low dose (2 mg) ziprasidone IM group. Therefore, observations could only be made regarding the dose response when comparing the low and high doses in each of these studies. Alternative strategies for review would be to pool the 2 mg IM control groups into the denominator of all ziprasidone treatment groups; however, this method may dilute safety data within the therapeutic dosage range.

In the ISS, the sponsor chose to submit tables which pooled together the three studies which they termed "fixed dose" studies. These included the two controlled studies (125 and 126) and study 121, an open label study testing 5, 10, & 20 mg (qid x 3 days) ziprasidone IM with a haloperidol treatment arm. The pooling of this data presented many unbalances given the different designs and duration of the studies (both studies 125 and 126 were 24 hours and study 121 was a three day study). The sponsor used this pooling to determine common adverse events for the proposed labeling comparing the ziprasidone treatment groups with haloperidol groups. This is discussed further in sections 8.1.5.3 and 8.1.5.4.

Although the ISS includes safety data pooling together patients who received IM treatment and subsequent oral treatment of ziprasidone, this review will focus primarily on the safety data of the IM treatment. It is noted that the adverse events were collected up to 24 hours after the last dose of IM medications and that some patients may have been receiving oral ziprasidone during some of that time period.

8.1.1 Deaths

There were no deaths reported as of the data cutoff date of July 31, 1998. However in the submission of 5/18/98, the sponsor reported one death (48 y.o. female: PID 127E-7190004) which occurred 74 days after discontinuing treatment with oral ziprasidone (100 mg bid x 162 days). No further details were provided.

8.1.2 Other Serious Adverse Events

In the Integrated Summary of Safety (ISS) the sponsor states that they applied the same definition for a serious adverse event that is used by FDA (i.e. any drug experience that is fatal or life-threatening, is permanently disabling, requires hospitalization, or is a congenital anomaly, cancer, or overdose). Serious adverse events were submitted as listings itemized by subjects and COSTART body system/preferred term.

Four of the five serious adverse events occurring during the phase I/II/III ziprasidone IM trials were listed as psychiatric events which may have been manifestations of the psychiatric disease under study. The following table summarizes the only serious adverse event reported during the phase I/II/III ziprasidone IM trials which was considered to be attributed to treatment with ziprasidone IM:

Serious adverse events IM dosing Phase I/II/III

SUBJECT #	AGE/ SEX	MEAN DOSE (MG)	# OF INJECTIONS/ TREATMENT (DAYS)	SERIOUS ADVERSE EVENT/ COMMENTS
125-7950071	67/M	2	1	Hypertensive episode 220/100 (sitting) 7 ½ hours after IM injection. Treated with captopril and clonidine. Subject had history of hypertension.

Please refer to Appendix 8.1.2 for serious adverse events which occurred during the extension studies in which patients were treated with oral ziprasidone.

8.1.3 Dropouts

8.1.3.1 Overall Profile of Dropouts

The primary integrated database included 99 (19%) of the total 523 patients who prematurely discontinued treatment in the Phase II/III trials from ziprasidone IM treatment groups. The sponsor's table below provides reasons for discontinuations:

Overview of Phase II/III Study Discontinuations All Phase II/III Studies				
Number (%) of Subjects	Ziprasidone 2mg* 92	Other Ziprasidone 431	Combined Ziprasidone 523	Haloperidol 142
Discontinuations				
Adverse event	6 (6.5)	17 (3.9)	23 (4.4)	2 (1.4)
Insufficient clinical response	6 (6.5)	14 (3.2)	20 (3.8)	3 (2.1)
Other	11 (12.0)	45 (10.4)	56 (10.7)	13 (9.2)
Total	23 (25.0)	76 (17.6)	99 (18.9)	18 (12.7)
(CONTINUED)				
* Subjects randomized to '2mg maximum Q10' group in protocols 125,126				
Other reasons for discontinuation may include failure to meet randomization criteria, lost to follow-up, protocol violation, withdrawn consent, etc.				
Protocols: 046,120,121,125,126,127E,306,306E				
Date of Table Generation: 06OCT97				

Number (%) of Subjects	Placebo 6
Discontinuations	
Adverse event	0
Insufficient clinical response	0
Other	0
Total	0

NOTE: "Other Ziprasidone" refers to all ziprasidone doses other than the ziprasidone 2 mg IM dose groups; "Combined Ziprasidone" includes all ziprasidone IM treatment groups.

It appears from the table above that the highest withdrawal rate for insufficient efficacy was seen in the 2 mg ziprasidone IM group, the low dose control group. However, please note that the above table, which was prepared by the sponsor, does not provide an accurate profile of the discontinuations. In the ISS text (p.22 and 35), the sponsor makes an attempt to explain the inconsistencies in their tables by stating that three subjects in the 2 mg ziprasidone IM group and four subjects in the "other ziprasidone" IM groups may have been counted as withdrawals for adverse events but latter considered to withdraw due to an insufficient clinical response. However, even with these corrections, there is still a discrepancy amongst the sponsors tables when compared with the table of line listings of withdrawals. It is possible that the

sponsor confused the number of events with the number of subjects who discontinued when making calculations for the above table.

8.1.3.2 Adverse Events Associated with Dropout

The following table was also included in the ISS and presents a count of discontinuations that is consistent with the table of line listings of withdrawals in the safety data base:

Discontinuations Due to Adverse Events During Intramuscular Dosing in Phase II/III Studies					
2 mg Ziprasidone 2 subjects discontinued		Other Ziprasidone 9 subjects discontinued		Haloperidol 1 subject discontinued	
Body System	Preferred Term	Body System	Preferred Term	Body System	Preferred Term
Cardiovascular	Hypertension	Body as a Whole	Suicide gesture	Nervous	Dystonia Extrapyramidal syndrome
Nervous	Agitation Psychosis	Cardiovascular	Hypertension Migraine Tachycardia		
Urogenital	Priapism	Nervous	Agitation Akathisia (2 cases) Personality disorder Psychosis Somnolence		
		Digestive	Nausea Diarrhea		
		Respiratory	Respiratory tract infection		
		Urogenital	Urinary tract infection		

Using figures from the table above, the rates of withdrawals from the entire safety data base are the following:

Rates for withdrawal for adverse events in the integrated safety data base for ziprasidone IM

	2 mg ziprasidone IM n=92	2.5-20 mg ziprasidone IM n=431	all ziprasidone IM n=523	Haloperidol n=142
# withdrawals	2 (2.2%)	8 (1.9%)	10 (1.9)	1 (0.7%)

It appears that the 2mg ziprasidone IM group, which was used as a low dose control group, demonstrated the highest rate of withdrawal for adverse events. This observation suggests that the low dose of 2 mg ziprasidone was not a true placebo.

Of note in the adverse events listed above is Subject 126-6380212, a 50 y.o. male patient with schizophrenia who experienced **priapism** after two doses of 2 mg ziprasidone IM. This patient was subsequently treated with epinephrine, cephalexin and a needle aspiration of blood from the corpora cavernosa. According to the case report form, this subject had 2 prior episodes of priapism (3 and 6 months prior to taking ziprasidone IM) and had one more episode one week after discontinuing ziprasidone IM requiring a surgical (Winters) procedure. The sponsor and the investigator attributed this episode of priapism to the subject's prior treatment with prolixin decanoate. The subject's prior treatment with prolixin decanoate are as follows:

16 days prior to start of trial: 25 mg IM prolixin decanoate
 14 days prior " " : 75 mg " "
 7 days prior " " : 75 mg " "

It is noted that the labeling for prolixin decanoate does not mention priapism as a warning or precaution. Although this subject's schedule for prolixin decanoate may have been on the higher end of dosing, the labeling allows for individual variation of treatment that is not inconsistent with this subject's dosing.

8.1.4 Other Search Strategies

None.

8.1.5 Common Adverse Events

8.1.5.1 Approach to Eliciting Adverse Events in the Development Program

Pfizer did not provide their working definition of an adverse event in the Integrated Summary of Safety. All adverse events presented were classified by organ system using COSTART terminology. The sponsor stated that adverse events were collected by either direct observation, by the investigator or by patients volunteering this information. This method may result in an under representation of adverse events, because the schizophrenic population may not be able to spontaneously volunteer and articulate their discomfort.

The ISS mentions that adverse events were collected up to 24 hours after the last dose of IM medications and that some patients may have been receiving oral ziprasidone during some of that time period.

8.1.5.2 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

In the ISS, the sponsor chose to submit tables which pooled together the three studies which they termed "fixed dose" studies. These included the two controlled studies (125 and 126) and study 121, an open label study with a haloperidol treatment arm (see section 8.1 for dosing schedules). The pooling of this data presented many unbalances given the different designs and duration of the studies (both studies 125 and 126 were 24 hours and study 121 was a three day study).

Appendix 8.1.5.2 delineates the adverse events occurring in 1% of patients taking 5-20 mg ziprasidone IM from the "fixed dose" studies (121, 125 and 126). In the 1% table for the proposed labeling, the sponsor established a comparison of ziprasidone IM and haloperidol by utilizing the columns of "Other Ziprasidone" and "Haloperidol" from Appendix 8.1.5.2.

Appendix 8.1.5.3 is extracted from the sponsor's proposed labeling and lists all adverse events occurring in the primary safety data base in the original submission. This list merges all adverse events in the oral and IM ziprasidone NDA data bases that have not been reported in the 1% tables or else where in the proposed labeling.

8.1.5.3 Identifying Common and Drug-Related Adverse Events

Because of the lack of a placebo-controlled study, the traditional approach to identify a common event as occurring at least 5 % in the treatment group and twice as frequently in the treatment group compared to placebo cannot be strictly applied. In the proposed labeling, the sponsor chose to define commonly observed events in this data base as occurring $\geq 5\%$ in the ziprasidone group from fixed dose studies (from studies 121, 125, & 126) and twice as frequently than in the haloperidol group (study 121). Using this approach, the sponsor identified **injection site pain, nausea and dizziness** as common events when comparing ziprasidone with haloperidol using the sponsor's criteria. However this approach may be inconsistent with the format of most labeling which identifies common adverse events as those that occur in the study drug groups compared to the incidence in placebo groups.

An alternative approach, if one were to assume that the low dose ziprasidone simulates a placebo group, would be to use this same pooled data from fixed dose studies (121, 125 and 126) and identify a common adverse event as one occurring in at least 5% of the higher dose group (5-20 mg ziprasidone IM) and more than twice as frequently in the higher dose group than in the low dose 2 mg ziprasidone IM control group. From this perspective, the drug related adverse events fulfilling this criteria were **tachycardia, headache** (of note, Subject 121-7590150 discontinued due to exacerbation of a migraine headache), **dyspepsia, nausea, vomiting, agitation, akathisia, anxiety, dizziness, and insomnia.**

8.1.5.4 Additional Analyses and Explorations

Dose Response

A dose relationship for several adverse events was established when the sponsor applied the Mantel-Haenszel test to the pooled data from the fixed dose studies (121, 125, 126) for doses of 2, 5, 10 and 20 mg ziprasidone IM. The sponsor's analysis showed a statistically significant dose relationship ($p \leq 0.05$) with the following adverse events: **postural hypotension, akathisia, nausea, constipation, increased salivation, and insomnia.**

Demographic Analyses

The sponsor did not include statistical comparison of the interaction effect of gender, age, or race for the pool of fixed dose ziprasidone studies (121, 125, and 126). Please see Appendix 8.1.5.4 for the sponsor's summary tables of comparisons of groups by gender, age and race. From observation, the most consistent finding was that female patients have more digestive system adverse events than males. Also from this data, it appears that the age group > 55 were more sensitive to cardiovascular and digestive adverse events at low doses than the younger age group; however, the population sample is not large enough to make definitive conclusions. There were no consistent findings comparing races.

8.1.6 Laboratory Findings

8.1.6.1 Extent of Laboratory Testing in the Development Program

The Integrated Summary of Safety (ISS) states that routine laboratory tests for all studies included complete blood count, electrolytes, serum hepatic and renal function. The final samples were collected at either six hours after the last dose administration or at the end of the twenty-four hour period (which ever was longer) or at early termination. The frequency of laboratory testing varied amongst the studies; the ISS merely states that routine laboratory tests were collected at baseline and repeated during and/or at the end of treatment.

8.1.6.2 Selection of Studies and analyses for Overall Drug-control comparisons

This section will discuss trends observed in the entire safety data base. Also reviewed are the two controlled studies 125 and 126 which utilized the low dose (2 mg) ziprasidone IM control group to help assess the effects of higher doses of ziprasidone.

8.1.6.3 Standard Analyses and Explorations of Laboratory Data

8.1.6.3.1 Analyses focused on Measures of Central Tendency

Please see Appendix 8.1.6.3.1 for the sponsor's table of the median change from baseline to last observation of laboratory values for all Phase II/III studies. The sponsor did not perform any statistical analysis of comparisons of any treatment group. Inspection shows that the triglycerides levels were elevated by 8% in all ziprasidone treatment groups when comparing median change from baseline to last observation. The low dose 2 mg ziprasidone IM group had a mean change of 4% in cholesterol levels while the higher ziprasidone groups showed a mean change of 1% from baseline.

Mean triglycerides were also noted to be elevated in all ziprasidone IM treatment groups in the controlled studies 125 and 126. In study 125, the median change from baseline to last observation of triglycerides increased by 17 % in the ziprasidone 2mg IM treatment group and increased by 35 % in the ziprasidone 10 mg IM treatment group. In study 126, triglycerides were noted to increase by 9 % in the ziprasidone 2 mg IM group and by 33.6 % for the ziprasidone 20 mg dose.

8.1.6.3.2 Analyses focused on Outliers

The sponsor used an elaborate system of assessing abnormal laboratory results. Different normal reference ranges were used for patients who had normal baseline values versus abnormal baseline values.

Appendix 8.1.6.3.2a contains the sponsor's laboratory reference ranges used to determine whether the baseline value was normal or abnormal; baseline values were then compared to post baseline values (it is unclear from the ISS if the post baseline values were the worst laboratory value found during the study). The sponsor applied different criteria for subjects who began the study with abnormal laboratory values. Clinical significance was determined using the values of column "A" and "B" Appendix 8.1.6.3.2b (extracted from review of NDA 20-825); for subjects with normal baseline values, the worst value was required to be outside the range specified in column "A." Meanwhile, for subjects with an abnormal baseline value, it was required that their post baseline lab value fulfill criteria of both column "A" and "B" in order to be considered of clinical significance and be included in the number of subjects with laboratory abnormalities.

Please refer to Appendix 8.1.6.3.2c for the incidence of clinically significant laboratory abnormalities for all ziprasidone IM Phase II/III studies. Laboratory abnormalities were observed in 16 % (14 patients of 90) of the 2 mg ziprasidone IM group and 19 % (78 of 403) of the higher dose IM ziprasidone treatment groups. Of note are the following incidents of clinically significant laboratory test abnormalities:

Adverse Event	Ziprasidone IM 2 mg n=90	Other ziprasidone IM doses n=403
↑ Eosinophils	2 (2%)	6 (1.5%)
↑ SGOT	1 (1)	0
↑ Potassium	1 (1)	5 (1)
↓ Phosphorus	0	2 (1)
↑ Phosphorus	1 (1)	6 (1.5)
↑ Triglycerides	4 (4)	24 (6)
↑ Urine glucose	1 (1)	8 (2)
↑ Urine WBC	5 (6)	12 (3)
↑ Urine RBC	2 (2)	6 (1.5)

The incidence of elevated triglycerides for study 125 showed an abnormality in 21% (11 of 53) of the 2 mg ziprasidone IM group and 23 % (14 of 62) of the 10 mg ziprasidone groups. Study 126 revealed that 13 % (5 of 38) of subjects in the 2 mg ziprasidone IM group had an elevated triglycerides while there was an incidence of 23% (9 of 40) who had abnormal changes in triglycerides compared to baseline. The results from studies 125 and 126 suggest that there is a dose effect of elevated triglycerides for administration of ziprasidone.

Also of note in the ziprasidone groups are the elevated urine WBC and RBC count. The haloperidol groups demonstrated an elevated urine WBC in 7% (7 of 94) of subjects in the integrated safety data base; elevated urine RBCs were not observed in the in the haloperidol group.

Proteinuria was observed in 25 % (4 of 16) of patients tested. Of note is subject 120-0747002 whose baseline value was 26.4 mg/day which elevated to 486.5 mg/day after three days of IM ziprasidone treatment. Other renal functions for this patient at the time were within normal limits; there is no follow up information provided for this patient.

Elevated bilirubin was noted in a 50 y.o. patient (046-05570029) who received 10 mg ziprasidone IM q 2 hours for 3 days. Baseline values were 0.6 mg/dl (NL: 0-1.3) and on day 4, his bilirubin was elevated to 2 mg/dl; his levels normalized by day 11.

8.1.6.4 Dropouts for Laboratory Abnormalities

There were no dropouts for laboratory abnormalities.

8.1.6.5 Additional Analyses and Explorations

Study 121, a Phase III open label 3 day fixed IM dose study, included renal function tests (urinary microalbumin, NAG:creatinine ratio, total protein, β 2-microglobulin) which were conducted at screening and Day 4 (i.e. within 24 hours of discontinuing IM medication). Appendix 8.1.6.4 summarizes these results which show comparable percentage of incidence across the ziprasidone and haloperidol treatment group. The sponsor reports that there were no clinically significant changes noted during the study.

8.1.7 Vital Signs

8.1.7.1 Extent of Vital Sign Testing in the Development Program

The ISS does not specify which vital signs were compared to baseline; the final vital sign monitoring was taken at least 6 hours after the final dose was administered. The sponsor analyzed changes in standing or sitting systolic or diastolic blood pressure and sitting or standing heart rate, and weight gain or loss. Please refer to Appendix 8.1.7.3.1 for vital sign parameters used to determine clinical significance. There is no data comparing changes of supine and standing vital signs; therefore, orthostatic changes could not be adequately assessed.

8.1.7.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The focus of this section will be trends observed in the integrated Phase II/III safety data base, study 121, (a phase III open label study of 20-80 mg/d ziprasidone IM x 3 days with one arm including treatment with haloperidol), studies 033 & 038 (both Phase I studies with normal subjects), and study 046 (Phase I studies with schizophrenic/schizoaffective patients).

8.1.7.3 Analyses and Explorations of Vital Sign Data

8.1.7.3.1 Phase I Studies

As part of the review process, Sughok K. Chun, M.D., cardiology consultant at FDA (review of 11/4/98) did an in depth review of vital signs in studies 033, 038 and 046. In study 033 (single dosing 5-20 mg ziprasidone IM in healthy males), standing blood pressure was unable to be recorded in three (of eleven) subjects because of dizziness upon standing; another subject (033-708-0001) experienced a one minute syncopal episode three hours after a 5 mg dose of ziprasidone IM requiring treatment of oxygen for 16 minutes. In study 038 (single dose study 5-20 mg ziprasidone IM in healthy males), four (of six) subjects taking 10 mg ziprasidone IM and six (of six) subjects taking 20 mg ziprasidone IM were unable to stand up for 0.5 to 2.0 hours after dosing. Dr. Chun concluded that severe orthostatic hypotension, most likely due to a decrease of systolic blood pressure and increase in heart rate, was observed in healthy males when exposed to ziprasidone IM.

In study 046 (multiple dosing 20-80 mg/d x 3 days in patients with schizophrenia or schizoaffective disorder), Dr. Chun noted an increase in heart rate (>120 bpm) at the following rates: placebo:16.7%; ziprasidone IM 20 mg/d:33.3%; ziprasidone IM 40 mg/d:57.1%; and, ziprasidone IM 80 mg/d:16.7%. Otherwise, mean changes from baseline for vital signs were not felt to be clinically significant in study 046. (Please refer to Appendix 8.1.7.3.1 and Dr. Chun's review for further details)

8.1.7.3.2 Phase II/III Studies

In her review of study 121 (a phase III open label study of 20-80 mg/d ziprasidone IM x 3 days with one arm including treatment with haloperidol), Dr. Chun reports that a "postural drop of systolic blood pressure

of 10-20 mmHg with significant increase of standing heart rate and diastolic blood pressure" was observed in most cases after each dosing, especially after doses of 10 and 20 mg ziprasidone IM. The following table (extracted from Dr. Chun's review) summarizes the incidences of clinically significant changes from baseline in the fixed dose studies (121, 125 and 126):

Subjects with clinically significant changes in BP/HR in studies 125, 125 and 121

(Table extracted from Cardiology Consult:10/23/98)

	Z 2mg QID		Z5,10, 20mg QID		Combined ZIPR		Haloperidol	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
StandSBP decrease	90	2 (2.2)	300	25 (8.3)	390	27 (6.7)	92	8 (8.7)
StandDBP increase	90	2 (2.2)	300	23 (7.7)	390	25 (6.4)	92	3 (3.3)
SitSBP decrease	92	1 (1.1)	303	10 (3.3)	395	11 (2.8)	94	3 (3.2)
SitDBP increase	92	0 (0.0)	303	19 (6.3)	395	19 (4.8)	94	5 (5.3)
StandHR increase	89	2 (2.2)	300	61(20.3)	389	63(16.2)	92	15(16.3)
SitHR increase	92	0 (0.0)	303	23 (7.6)	395	23 (5.8)	94	9 (9.6)

BP/HR measurements : Study 121 – BL 0, 30 & 60 min after IM dose;

Studies 125 & 125 – BL 0, 30 & 60 min after each dose and end point

Dr. Chun notes that the incidence of significant decreases of standing and sitting systolic blood pressure and the increase of standing heart rate and diastolic blood pressure are similar amongst the higher dose ziprasidone IM (5, 10, 20 mg) and the haloperidol group.

In the integrated safety data base, the following vital sign parameters occur with a greater incidence in the higher dose ziprasidone groups compared to the low dose (2mg) ziprasidone groups: 1) a decrease in standing and sitting systolic blood pressure, 2) an increase in standing and sitting diastolic blood pressure, and 3) an increase in standing and sitting heart rate (see Appendix 8.1.7.3.2). The incidence of increased heart rate was observed in 18.4% (76 of 412) of patients in the higher dose ziprasidone IM group, compared to 2.2% (2 of 89) of the ziprasidone IM group and 13 % (17 of 131) of the haloperidol group.

8.1.7.3.3 Dropouts for Vital Sign Abnormalities

The following table summarizes all patients who withdrew due to vital sign abnormalities:

Subjects who discontinued due to vital sign abnormalities

Subject ID #	Age/Sex	Mean dose/ duration (Ziprasidone Rx group)	Reason for d/c	Outcome/comments
121-5650217	M/36	70 mg/ 2 days (20 mg qid)	tachycardia	Heart beat: At baseline: 92 bpm Maximum : 136 bpm (30 min. after 2 nd injection):
125-7950071	M/67	2 mg/ 1 day (2 mg group)	hypertension	Baseline: 125/85 mmHg (sitting) Time after 1 st injection: 2.5 hrs: 140/92 3 hrs: 170/100 7 hrs: 200/100 8 hrs: 220/100
306-3540106	F/55	30 mg/ 2 days (10 mg qid)	hypertension	Baseline: 130/70 (sitting) 1 hr after 6 th injection: 170/120

8.1.8 ECGs

8.1.8.1 Extent of ECG testing in the development program

ECGs were recorded in all Phase II/III trials. The tracing were read on site for most of the studies and then re-read at a central site at Premier Research Worldwide which the sponsor states was blinded to the study drug group. The local and centrally read ECGs were included in the study report of studies 046 and 306. However, the study report for study 120 contains only the on site ECG reading. The ECGs for studies 121, 125, 126 and 127E were only read once at the central site. Only centrally read ECG data was included in the sponsor's integrated safety tables.

8.1.8.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

This section will discuss observations seen in study 121 (a Phase III open label study with a haloperidol treatment arm) as well as ECG tracing in study 046 (a Phase I open label study in psychiatric patients).

8.1.8.3 Analyses and Explorations of ECG Data

8.1.8.3.1 Individual Studies (046 and 121)

A review of all of the protocols of the studies in this NDA data base revealed that most ECGs were recorded at trough levels of ziprasidone (e.g. 6-24 hours after administration of the study drug). Study 046 (multiple dose study, 20-80 mg/d x 3 days in stable psychotic patients) obtained ECGs at baseline, 1 hour after the first dose (at approximate C_{max}), and on day 4, approximately 18 hours after the last dose of day 3. Referring to results seen in Appendix 8.1.7.1 (and summarized below), Dr. Chun, cardiology consultant, concludes that this data demonstrates a trend of QT prolongation:

Summary of QTc Mean changes from baseline (Study 046)

	Ziprasidone IM (mg/day)			Placebo
	20 (n=6)	40 (n=6)	80 (n=6)	(n=6)
QTc: Day 2 1 hr post 4 th dose	4 msec	11 msec	13 msec	5
QTc: Day 4 18 hrs after last dose of day 3	-4 msec	22 msec	19 msec	1

It appears that there is a dose dependent relationship when viewing the QTc trends at the reading during day 2 recorded at the approximate t_{max}.

For Study 046, Dr. Chun also concluded that there were no significant changes in the PR or QRS duration as a result of exposure to ziprasidone IM (see Appendix 8.1.8.3a).

Appendix 8.1.8.3b (submission 10/19/98) summarizes QTc changes observed in study 121 (a phase III open label study of 20-80 mg/d ziprasidone IM x 3 days with one arm including treatment with haloperidol). There is a discrepancy in the timing of the ECGs as presented in the submission of 10/19/98 (requested by Dr. Chun) and in the original NDA submission of 12/18/97. In the study protocol and study report for study 121, the only ECGs scheduled to be conducted were at screening, day 4 (prior to oral ziprasidone) and at day 7; however, the submission of 10/19/98 suggests that there was an additional ECG performed on day 1, one hour post dosing of the first IM dose. From her review of study 121, Dr. Chun concludes that that most ECG abnormalities and the number of clinically significant changes in QTc interval observed were "small and comparable across all treatment groups...most of the abnormal ECG finding during IM treatment were flattening T wave, and/or right axis deviations and/or nonspecific ST/T abnormalities."

8.1.8.3.2 Analyses focused on Outliers

The number of clinically significant QTc interval changes in the entire safety data base is summarized in the following table from the sponsor's ISS:

QTc Interval	Number (%) of Subjects with a Clinically Significant Change in QTc Interval During IM or IM Plus Oral Treatment					
	2 mg Ziprasidone		Other Ziprasidone		Haloperidol	
	IM	IM Plus Oral	IM	IM Plus Oral	IM	IM Plus Oral
≥ 450 msec	8(8.7)	10(10.9)	22(5.2)	39(9.2)	12(9.3)	16(11.7)
≥ 480 msec	0	0	2(0.5)	3(0.7)	0	0
≥ 500 msec	0	0	1(0.2)	1(0.2)	0	0
Increase in QTc Interval						
≥ 50 msec	0	0	7(1.7)	13(3.1)	4(3.1)	7(5.2)
≥ 75 msec	0	0	1(0.2)	2(0.5)	0	0
≥ 100 msec	0	0	0	0	0	0
≥ 20%	0	0	0	1(0.2)	0	0

The following table from the sponsor's ISS summarizes details of the four subjects whose QTc interval changes were ≥ 480 msec had a change of ≥ 75 msec:

Clinically Significant ECG Readings					
Subject ID	Study drug randomization group	Baseline	Most abnormal QTc interval	QTc change from Baseline	Day of Abnormality
QTc of ≥ 480 msec					
121 05810008	Ziprasidone, 20 mg	444 msec	484 msec	40 msec	4 (IM dosing)
127E0701003	Ziprasidone, 20 mg	426 msec	490 msec	64 msec	7 (oral dosing)
121 05900362	Ziprasidone, 5 mg	420 msec	504 msec	84 msec	4 (IM dosing)
QTc increase of ≥ 75 msec					
306E03740017	Ziprasidone	331 msec	414 msec	83 msec	42 (oral dosing)
121 05900362	Ziprasidone, 5 mg	420 msec	504 msec	84 msec	4 (IM dosing)

8.1.8.3.3 Dropouts for ECG Abnormalities

There were no dropouts for ECG.

8.1.9 Special Studies

8.1.9.1 Sulphobutylether Beta-Cyclodextrin (SBECD)- the excipient

Sulphobutylether Beta-Cyclodextrin (SBECD) is a novel excipient not currently used in any marketed formulation.

SBECD is also being studied to be an excipient in the drug development of an IV formulation, which is still in early phases of drug development. The sponsor included safety data obtained from the work-up of SBECD as an excipient to this IV. There were 4 studies with data of SBECD administered alone: 1) Study 225 (SBECD alone n=10), a single blind placebo controlled IV study with doses of 25 mg/kg to 200 mg/kg, 2) Studies 226 (SBECD alone: n=9), 227 (SBECD alone: n=9), and 230 (SBECD alone: n= 21), studies in which SBECD IV was used as the placebo control compared to SBECD in combination with the active IV formulation.

The sponsor calculated that each milliliter of the ziprasidone IM formulation contains 20 mg ziprasidone, 294 mg SBECD and 4.7 mg of methanesulfonate. If patients were to be receiving 20 mg ziprasidone IM qid for each dose with a maximum of 4 doses in one day, they could potentially be exposed to 1176 mg daily of SBECD. Assuming that subjects range 50-70 kg, the exposure could be determined to be ranging from 17 to 24 mg/kg/day which appears to be comparable to dosing exposure in the phase I studies of IV antibiotic formulation.

Pharmacokinetic data has shown that SBECD is eliminated by the kidney. Adverse events in the submitted in these studies included abnormal vision, dizziness, headache, mild elevation in AST, and rash. The study report for study 150-230 also mentions two subjects with hematuria during exposure to SBECD, but with normal baseline.

No studies were conducted that tested the IM form of SBECD (without the ziprasidone IM formulation) and its behavior at a muscular injection site.

8.1.9.2 Extrapyramidal Symptoms

Extrapyramidal Symptoms (EPS) will not be reviewed in depth for ziprasidone IM as there is sufficient evidence from the review of the oral formulation that ziprasidone has the potential to cause EPS (see review NDA-20-825:4/30/98). Of note, four patients in the ziprasidone IM data base discontinued due to symptoms of EPS: 1) Subject 121-5980101 withdrew on the first day of treatment with ziprasidone IM (10 mg qid) because of akathisia, sedation and increased psychosis and 2) Subject 125-6530077 withdrew on the first day of treatment with ziprasidone IM (10 mg qid) after 2 injections due to akathisia, diarrhea and nausea, 3) Subject 121-5980101 experienced acute dystonia on the first and second day of treatment with ziprasidone IM (10 mg qd and 5 mg qd respectively), and withdrew because of laryngospasm on the third day just after starting oral ziprasidone 40 mg qd, and 4) Subject 121-5980101 withdrew on the first day of treatment with ziprasidone IM (10 mg qid) because of akathisia, sedation and increased psychosis.

8.1.10 Withdrawal Phenomena/Abuse Potential

The sponsor did not study the abuse potential nor the effects of sudden or gradual discontinuation of ziprasidone IM treatment.

8.1.11 Human Reproduction Data

The sponsor did not address this topic in the Integrated Summary of Safety, and this information was not located in this submission.

8.1.12 Overdose Experience

There was no report regarding overdose of ziprasidone IM in the ISS.

8.2 Adequacy of Patient Exposure and Safety Assessments

8.2.1 Adequacy of Clinical Experience

The clinical data of this NDA is based on a relatively small subject exposure of the adult population for a new molecular entity. ~~The labeling proposed is combined with the previously proposed labeling for the oral formulation of ziprasidone.~~ However, the oral formulation was not approved for commercial marketing because of cardiovascular safety issues. Therefore, the current ziprasidone intramuscular exposure of the adult population appears to be insufficient to merit marketing with its own labeling. There was no pediatric exposure of ziprasidone IM reported in this NDA submission.

The sponsor submitted more than one adequate and well controlled study to support the efficacy claims of ziprasidone IM.

8.2.2 Adequacy of Animal and/or In Vitro Testing

Toxicity studies were not adequately performed using the intramuscular formulation of ziprasidone; preclinical studies were performed using the IV and oral formulations without adequate pharmacokinetic data to generalize results to the IM formulation of ziprasidone. Also, reproductive studies and

genotoxicity studies were not performed using the entire formulation of ziprasidone IM which would include, according to the proposed labeling, the excipient Sulphobutylether Beta-Cyclodextrin (SBECD), methanesulfonic acid and ziprasidone. For further details, please refer to Dr. Freed's Pharmacology Review.

8.2.3 Adequacy of Routine Clinical Testing

This submission was of adequate quality to be submitted for review. Of concern, though, is that most of the ECG recordings obtained in this data base were performed without regard for timing. There were few ECG readings/QTc measurement done at times of peak concentrations of ziprasidone IM.

Ziprasidone IM was not tested on patients with hepatic or renal impairment. This becomes a note of concern because the cyclodextrin excipient is cleared by renal filtration. The sponsor included a mention of this precaution under the special populations section in the proposed labeling.

There was also a methodological flaw in the collection of the vital signs. Most of the vital signs recorded were done with sitting blood pressure rather than blood pressures recorded in the supine position; this does not allow for the most accurate assessment of orthostatic effects of ziprasidone. Also, in looking at the median changes from baseline of vital signs, the sponsor used observations that could have been recorded up to twenty-four hours after the last dose of study treatment; this may provide less accurate comparisons than could have been made if these measurements were recorded sooner given the half-life of this drug ($t_{1/2}$ was approximately 3 hours).

The elaborate system used by the sponsor for reporting clinical significance of laboratory values set up many restrictions that may not have captured laboratory abnormalities of interest. The criteria for a change from baseline for a baseline-abnormal subject appears extreme, and changes that may be concerning would not be picked up using this system. It would perhaps be more helpful to identify changes from baseline and use that as the criteria. It is curious that there were a significant number of subjects who had an abnormal baseline to merit different criterion; however, their laboratory values were not so abnormal that they were excluded from enrolling in the study. Also of note is that the last laboratory value was performed up to 24 hours after the last administration of IM ziprasidone, some subjects may no longer have had appreciable plasma concentrations when the tests were performed, and the maximum effect of the study drug may not have been appreciated.

8.2.4 Adequacy of Metabolic Workup

A metabolic profile of ziprasidone IM was not performed. It is unknown if the combination of the ingredients in the entire formulation of ziprasidone IM (SBECD, methanesulfonic acid and ziprasidone) would generate metabolites that were not identified in the metabolic work up of oral ziprasidone.

8.2.5 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by New Drug; Recommendations for Further Study

Because of ziprasidone's potential to prolong the QTc interval, it would be helpful to assess ECG monitoring more closely with a Holter monitor or a series of ECGs to assess QTc changes during concentration peaks.

8.2.6 Assessment of Quality and Completeness of Data

No electronic data sets were made available as part of the electronic submission, and all data was assessed from the grouping done by the sponsor's tables. Therefore, the laboratory abnormalities were determined by the sponsor's fixed criterion.

Some topic presentations within the NDA submission presented inconsistent data. The sponsor included several tables of the rate of discontinuations that were not consistent (see Section 8.1.3.1). Also, there were inconsistencies in the submission of the timing of cardiovascular data study 121 (see Section 8.1.8.3.), and

Dr. Chun, cardiology consultant noted paradoxical blood pressure data in study 033 (see Cardiology Consultant Review).

8.3 Summary of Selected Drug-Related Adverse Events

8.3.1 QTc prolongation

Ziprasidone IM has been shown to prolong the QTc interval in study 046, a multiple dose study in stable psychotic patients (See Section 8.1.8.3, p.21). **This potential to prolong the QTc has been established in the oral formulation of ziprasidone.** It is important to mention that most of the ECG work up for this NDA data base was done with little regard for the timing of the ECG or the effect of ziprasidone on the QTc at peak concentration. Drug induced QTc prolongation may be correlated with the development of ventricular arrhythmia, syncope, and sudden death.

Clinically significant QTc prolongation was noted in two patients while taking ziprasidone IM: 1) Subject 590-0362 had a QTc > 500 with an 84 msec change from baseline, and 2) Subject 121-5900362 had a 40 msec change from baseline (See section 8.8.3.2, p. 21).

Based on the findings which suggest that ziprasidone IM and oral ziprasidone prolong the QTc interval, Dr. S. Chun, FDA cardiology consultant (HFD-110), agreed with Dr. C. Ganley, FDA cardiology consultant for oral ziprasidone, that there may be the usual risks of ventricular arrhythmia, syncope, and sudden death observed with drugs which prolong the QT interval. It was recommended that the labeling clearly reflect this risk and that it may be necessary to consider this drug as a second line therapy if approved.

8.3.2 Orthostatic Hypotension/Syncope

Because ziprasidone demonstrates alpha adrenergic properties, it is not unexpected that orthostatic hypotension and syncope were observed as adverse events in this data base (see Section 8.1.7.3, p.19). It is noted that the most severe cases of orthostatic hypotension were observed in the Phase I studies in subjects who were naïve to neuroleptic exposure. However, in this NDA data base, there was also a significant incidence of decreases in systolic blood pressure, and increases in standing heart rates/diastolic blood pressure which suggests that ziprasidone IM also causes postural hypotension in patients previously exposed to neuroleptics.

It is also noted that there was a dose response relationship of postural hypotension observed (see Section 8.1.5.4, p. 16).

8.3.3 Tachycardia

Increases in standing and sitting heart rates were observed with a higher incidence in the higher dose ziprasidone IM groups (5-80 mg/day) compared with the low dose ziprasidone IM group (2mg/dose) in the integrated safety data base and in study 121, a phase III open label study of 20-80 mg/d ziprasidone IM (see Section 8.1.7.3.2, p.19).

One patient (subject #121-565-0217) discontinued due to an episode of tachycardia occurring within 30 minutes after the second injection of ziprasidone IM (see Section 8.1.7.3.3, p.20).

8.3.4 Priapism

One 50 y.o. male diagnosed with schizophrenia was noted to experience priapism after two doses of 2 mg ziprasidone IM (see Section 8.1.3.2, p.15). Although this subject's history suggests that he had a pre-disposition to priapism, there appears to be temporal relationship between the onset of symptoms of the reported episode and the administration of the second dose of ziprasidone. This event would merit a cautionary statement in labeling.

8.3.5 Elevated Triglycerides

Triglyceride levels were noted to be elevated in the median change from baseline to last observation of laboratory values for all Phase II/III studies (see Section 8.1.6.3.1, p. 17). In the two low dose ziprasidone IM controlled studies (studies 125 and 126), triglycerides were elevated from baseline to last observation. Results also suggested a dose response relationship in the two controlled studies 125 and 126, because the higher doses demonstrated higher elevations than the low dose groups (see Section 8.1.6.3.1, p. 17).

8.3.6 Extrapyramidal Symptoms (EPS)

Extrapyramidal Symptoms (EPS) was not reviewed in depth for ziprasidone IM as there is sufficient evidence from the review of the oral formulation that ziprasidone has the potential to cause EPS (see review NDA-20-825:4/30/98). There were four subjects who withdrew because of symptoms of EPS (see Section 8.1.9.2, p.23).

Akathisia was noted to have a dose response relationship (see Section 8.1.5.4, p.17).

9.0 Labeling

If approved, the sponsor's labeling will require considerable revision, especially in light of the fact that the proposed labeling is based entirely on the oral formulation, which was not approved for marketing. Please see section 8.3 for important concerns that will need to be addressed in future proposed labeling.

10.0 Conclusions

A nonapprovable letter was sent to Pfizer for NDA 20-825 on June 17, 1998 indicating that ziprasidone's ability to prolong the QTc interval presented a risk of potentially fatal ventricular arrhythmias which did not outweigh the benefits of ziprasidone compared to already marketed antipsychotics. Also of note was the high sudden death rate observed within the NDA data base.

The current submission of ziprasidone IM suggests that this formulation also has the potential for QTc prolongation. As with the ziprasidone oral NDA submission, the ziprasidone IM NDA submission had most of the ECGs performed at trough levels. During the one study done according to protocol, a dose dependent relation of QTc prolongation was observed when the QTc was measured at the approximate time of maximum concentration. It is important that the sponsor adequately characterize ziprasidone's effect on the QT interval by Holter monitor or multiple ECGs, encompassing a time period that would capture the individual variation of maximal concentrations that would be observed amongst patients in a clinical setting.

More understanding and research (using consistent methodology) are needed to clarify this issue for ziprasidone. There is evidence that, like the oral formulation, the intramuscular formulation of ziprasidone has the ability to prolong the QTc in a dose dependent manner within the therapeutic dosing range.

11.0 Recommendations

Ziprasidone IM has been shown to be effective for the indication of agitation in psychotic psychiatric patients.

However, it is important to note that the entire proposed labeling for ziprasidone IM is integrated with and based on the proposed labeling for the oral formulation, which is not approved for marketing. The exposure of adult population for this current submission is too small to merit marketing ziprasidone IM as a new molecular entity. The issue of approval for this new molecular entity becomes even more complicated when considering that the extent of the QTc prolongation of ziprasidone is not well characterized for both the oral and the intramuscular formulation; thus the risk for syncope, ventricular arrhythmias, and sudden unexpected death remains unknown. Therefore, it is recommended that the intramuscular formulation of ziprasidone not be approved at this time.

Roberta L. Glass 11/13/98

Roberta L. Glass, M.D.

Medical Officer, Division of Neuropharmacological Drug Products

NDA 20-919

Div File

HFD-120:Laughren/Hardeman/Mosholder/Glass

12-8-98

*I agree that this NDA
should not be approved
at this time. See memo
to file for more detailed
comments.*

James P. Laughren, MD
TL, PDP

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Appendix 5.1.1.1 Summary of all trials in integrated safety data base (from sponsor's submission 12/18/97)

Table H.2.1 Safety Database: Summary of All Studies Included in the Submission		Page 1 of 1				
	Studies Included in the Subject Count	Ziprasidone 2mg*	Other Ziprasidone	Combined Ziprasidone	Haloperidol	Placebo
Phase II/III Studies						
Fixed Dosing						
One day IM dosing	125, 126	92	104	196		
IM and oral dosing; haloperidol-controlled	121		206	206	100	
Flexible Dosing						
IM and oral dosing; haloperidol-controlled	306		90	90	42	
IM and oral dosing	120		12	12		
Patient pharmacokinetic study	046		19	19		6
Oral Extension Studies	127E, 306E	55 [55]	97 [97]	152 [152]	4 [4]	
Grand Total		92	431	523	142	6

* Subjects randomized to "2mg maximum QID" group in protocols 125,126
Numbers in brackets represent the number of subjects included in the non-bracketed number whose participation was in a continuation study under the same treatment as the parent study and are also counted in the parent study category for that treatment. These subjects are counted only once in totals and subtotals.

Appendix 5.1.1.2 Table of all Phase I/II/III studies (from sponsor's submission 12/18/97)

Summaries of Important Information from Completed Studies in the Ziprasidone Intramuscular Clinical Program	
Phase I Studies	
128-033-nonUS	Investigator blind, randomized, parallel, placebo-controlled, IM trial; healthy men; single dose; (ziprasidone: 5 mg, n=5; 10 mg, n=5; 20 mg, n=6; placebo: n=5); tartrate salt.
128-037-US	Open, randomized, 3-way crossover, oral/IM/IV trial; healthy men (n=13); single dose; ziprasidone doses (5 mg IM; 5 mg IV; 20 mg oral); mesylate salt.
128-038-US	Investigator blind, randomized, parallel, placebo-controlled, IM trial; healthy men; single dose; (ziprasidone: 5 mg, n=6; 10 mg, n=6; 20 mg, n=6; placebo, n=6); mesylate salt.
128-046-US	Investigator blind, randomized, parallel, placebo-controlled, IM trial; 20 men and 5 women with psychotic disease; multiple dose; (ziprasidone: 20 mg daily, n=6; 40 mg daily, n=7; 80 mg daily, n=6; placebo: n=6); mesylate salt.
Phase II/III Studies	
128-120-nonUS	Open-label, flexible-dose, IM (3 days) and oral (2 days) in 12 men with psychosis (ziprasidone IM 2.5-20 mg BID-QID; ziprasidone oral 20-60 mg BID).
128-121-US and Canada	Open, randomized, parallel, haloperidol-controlled, IM (3 days) and oral (4 days) trial; 271 men and 35 women with psychotic disorder (ziprasidone IM 5 mg QID, n=69; 10 mg QID, n=71; 20 mg QID, n=66; haloperidol IM up to 10 mg BID to QID, n=100); (ziprasidone oral 40-200 mg daily, BID schedule; haloperidol oral flexible daily dose, BID schedule).
128-125-US	Double-blind, randomized, parallel, IM, 24-hour study in 81 men and 36 women with acute agitation and psychotic disorder (ziprasidone IM 2 mg up to QID, n=54; 10 mg up to QID, n=63)
128-126-US	Double-blind, randomized, parallel, IM, 24-hour study in 62 men and 17 women with acute agitation and psychotic disorder (ziprasidone IM 2 mg up to QID, n=38; 20 mg up to QID, n=41)
128-306-nonUS	Open, randomized, parallel, flexible-dose, IM and oral study in 123 men and 9 women with acute agitation and psychotic disorder (ziprasidone: n=90; IM 5-20 mg/injection up to 4x/day; oral, 40-100 mg BID) (haloperidol: n=42; IM 2.5-10 mg up to 4x/day; oral, 5-40 mg BID); 1-3 days IM; oral to total 7 days study treatment.

Appendix 5.1.1.3 Table of trials testing the excipient SBECD (from sponsor's submission 12/18/98)

Number of Subjects Treated in Studies with Sulphobutylether Beta-Cyclodextrin					
Study	Treatment	Study Design	Number of Subjects		SBECD IV Clinical Database
		IV Dosing	per Group		SBECD
150-225 Single-Blind	SBECD	Single, escalating doses of 25, 50, 100 and 200 mg/kg SBECD and a single random dose of placebo during 5 study periods.	10		10
150-226 Single-Blind	SBECD	Single dose of 50 or 100 mg/kg SBECD.	50 mg/kg	3	8
			100 mg/kg	5	
150-227 Open-Radiolabel	SBECD	IV infusion over 1 hour of 100 mg/kg SBECD on day 1 followed 12 hours later by IV infusion of 100 mg/kg SBECD. 50 mg/kg SBECD IV infusion BID on days 2-9. Single 50 mg/kg SBECD IV infusion on day 10.	9		9
150-230 Double-Blind	SBECD	Cohort 1: 96 mg/kg SBECD IV BID on day 1 and 48 mg/kg IV BID days 2-7. 96 mg/kg SBECD IV BID on day 21 and 80 mg/kg IV BID on days 22-27.	Cohort 1	14	14
		Cohort 2: 96 mg/kg SBECD IV BID on day 1 and 64 mg/kg IV BID days 2-7.	Cohort 2	7	7
SUBJECT TOTAL					48

Appendix 5.1.2.1 Demographics of subjects exposed to ziprasidone in Phase I clinical trials (from sponsor's submission of 8/23/98)

Demographic Characteristics for Ziprasidone studies 033, 037 and 038				
	Ziprasidone 5mg IM	Ziprasidone 10mg IM	Ziprasidone 20mgIM	Placebo
	Male	Male	Male	Male
Number of Subjects	24	11	12	11
Age (years):				
18-25	10	1	6	3
26-35	11	7	3	2
36-45	2	3	3	6
Mean age (years)	27.2	31.3	28.2	33.5
Age range	19 - 42	22 - 45	18 - 43	20 - 44
Race:				
Asian	0	0	0	0
Black	0	0	0	0
White	21	11	11	11
Other	1	0	0	0
Mean weight (kg)	76.9	77.8	77.8	73.9
Weight range	63 - 97	72 - 87	72 - 86	63 - 83

Appendix 5.1.2.2 Demographics of subjects exposed to the excipient Sulphobutylether Beta-Cyclodextrin (SBECD) clinical trials (from sponsor's submission of 8/23/98)

Demographic Characteristics for SBECD Studies 150-225, 150-226, 150-227 and 150-230					
Study Number	150-225	150-226	150-227	150-230	Total
Number of SBECD Subjects	10	8	9	21	48
Age (years)					
<18	0	0	0	0	0
18 - 24	3	3	0	14	20
25 - 34	3	1	0	7	11
35 - 44	3	4	9	0	16
≥ 45	1	0	0	0	1
Age range (years)	22 - 45	22 - 44	35 - 44	18 - 34	18 - 45
mean	32	31	39	24	31.5
Race					
White	10	8	9	20	47
Other				1	1
Weight range (kg)	64.0 - 81.6	33.5 - 87.0	53.6 - 81.9	59.6 - 92.8	59.6 - 92.8
mean	72.3	73.0	75.2	73.5	73.5
Sex					
Male	10	8	9	21	48
Female	0	0	0	0	0

Appendix 5.1.2.3 Demographics of subjects exposed to ziprasidone in Phase II/III clinical trials (from sponsor's submission of 12/18/97)

Demographic Characteristics All Phase II/III Studies									
	Ziprasidone 2mg*			Other Ziprasidone			Combined Ziprasidone		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects	68	24	92	369	62	431	437	86	523
Age (years):									
18-54 years	64	22	86	343	52	395	407	74	481
>=55 years	4	2	6	26	10	36	30	12	42
Mean age (years)	37.3	42.0	38.6	37.5	42.1	38.2	37.5	42.1	38.2
Age range	18-67	24-71	18-71	19-76	21-66	19-76	18-76	21-71	18-76
Race:									
Asian	2	1	3	6	0	6	8	1	9
Black	15	5	20	94	17	111	109	22	131
Caucasian	44	18	62	239	43	282	283	61	344
Other	7	0	7	30	2	32	37	2	39
Mean weight (kg)	82.2	81.0		80.4	77.0		80.7	78.1	
Weight range	53-127	51-104		42-154	41-113		42-154	41-113	

(CONTINUED)
 * Subjects randomized to '2mg maximum BID' group in protocols 125,126
 Protocols: 046,120,121,125,126,127E,306,306E
 Date of Table Generation: 04OCT97

Demographic Characteristics All Phase II/III Studies						
	Haloperidol			Placebo		
	Male	Female	Total	Male	Female	Total
Number of Subjects	127	15	142	5	1	6
Age (years):						
18-54 years	122	14	136	5	1	6
>=55 years	5	1	6	0	0	0
Mean age (years)	36.3	45.0	37.2	42.8	41.0	42.5
Age range	19-62	37-57	19-62	40-48	41-41	40-48
Race:						
Asian	4	0	4	0	0	0
Black	35	2	37	0	1	1
Caucasian	79	13	92	5	0	5
Other	9	0	9	0	0	0
Mean weight (kg)	80.9	83.1		93.6	55.8	
Weight range	46-134	48-130		81-108	56-56	

* Subjects randomized to '2mg maximum BID' group in protocols 125,126
 Protocols: 046,120,121,125,126,127E,306,306E
 Date of Table Generation: 04OCT97

Appendix 5.1.3.1 Modal daily dose of ziprasidone IM in phase I studies (from sponsor's submission 8/3/98)

Modal Daily Dose and Duration of Ziprasidone Treatment for studies 033, 037 & 038						
	Modal Total Daily Dose Per Subject					Total of IM subjects (%)
	5mg IM	10mg IM	20mg IM	5mg IV	20mg Oral	
Number of Subjects with Treatment Duration						
<=1 day	24	11	12	11	12	47 (100.0)
2 - 7 days	0	0	0	0	0	0 (0.0)
8 - 14 days	0	0	0	0	0	0 (0.0)
Number of Subjects (%)	24 (51.1)	11 (23.4)	12 (25.5)	11 (NA)	12 (NA)	47 (100.0)
Mean Duration	1	1	1	1	1	1
Range	1 - 1	1 - 1	1 - 1	1 - 1	1 - 1	1 - 1

Studies 033, 037 and 038 were all single dose phase I studies in normal healthy male volunteers. Study 037 was a 3-way crossover study with an I.V. and P.O. leg, as well as an I.M. leg. The totals in this table only include the data from IM dosing leg of protocol 037. Study 033 used a research formulation (ziprasidone tartrate) while studies 037 and 038 used the commercial formulation (ziprasidone mesylate).

Appendix 5.1.3.2 Modal daily dose of SBECD in phase I studies (from sponsor's submission 8/3/98)

Modal Daily Dose and Duration of SBECD treatment for studies 150-225, 150-226, 150-227 & 150-230							
	Modal Total Daily Dose Per Subject (IV dose per body weight)						Total (%)
	25mg/kg	50mg/kg	86 - 100mg/kg	128 mg/kg	160mg/kg	200mg/kg	
Number of Subjects with Treatment Duration							
<=1 day	10	13	15	0	0	10	48 (52.2)
2 - 7 days	0	0	14	7	14	0	35 (38.3)
8 - 14 days	0	0	9	0	0	0	9 (9.3)
Number of Subjects (%)	10 (10.9)	13 (14.1)	38 (41.3)	7 (7.6)	14 (15.2)	10 (10.9)	92 (100.0)
Mean Duration	1	1	5	7	7	1	4
Range	1 - 1	1 - 1	1 - 10	7 - 7	7 - 7	1 - 1	1 - 10

Subjects in study 230 were dosed with a 96mg/kg BID loading dose followed by 48mg/kg, 64mg/kg or 80mg/kg. The 48mg/kg group (96mg/kg total daily dose per body weight) has been combined with the 120mg/kg data from studies 226 and 227.

Appendix 5.1.3.3 Mean daily dose of ziprasidone IM in phase II/III studies (from sponsor's submission 12/18/97)

Mean Daily Dose of Intramuscular Ziprasidone All Phase II/III Studies						
	Mean Daily IM Dose Per Subject				Total (%)	
	<5mg	>=5 to <40mg	>=40 to <60mg	>=60mg		
Number of Subjects with Treatment Duration						
1 day	40	107	10	0	157	(30.0)
2 days	45	63	6	2	116	(22.2)
3 days	0	105	73	67	245	(46.8)
>3 days	0	3	2	0	5	(1.0)
Number of Subjects (%)	85 (16.3)	278 (53.2)	91 (17.4)	69 (13.2)	523	(100.0)
Mean Duration	2	2	3	3	2	
Range	1-2	1-4	1-4	2-3	1-4	
Protocols: 046,120,121,125,126,127E,306,306E						
Date of Table Generation: 25NOV97						

Appendix 7.2.1.1 INVESTIGATORS AND STUDY CENTERS
(FROM SPONSOR'S PROTOCOL Study 125)

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Appendix 7.2.1.2 (from sponsor's submission)

Total Number of Injections by Timepoint - All Subjects, Observed Cases
Ziprasidone Protocol 125

Treatment Group	Hours Post First Dose	Number (%)* of Subjects with 1, 2, 3, or 4 Injections				Mode (Mean)
		1	2	3	4	
Ziprasidone 2 mg	0-2	54 (100.0)				1.0 (1.0)
	0-4	40 (74.1)	14 (25.9)			1.0 (1.3)
	0-6	26 (48.1)	27 (50.0)	1 (1.9)		2.0 (1.5)
	0-8	21 (38.9)	31 (57.4)	2 (3.7)		2.0 (1.6)
	0-10	20 (37.0)	27 (50.0)	6 (11.1)	1 (1.9)	2.0 (1.8)
	0-12	20 (37.0)	26 (48.1)	6 (11.1)	2 (3.7)	2.0 (1.8)
	0-16	16 (29.6)	22 (40.7)	14 (25.9)	2 (3.7)	2.0 (2.0)
	0-20	14 (25.9)	17 (31.5)	15 (27.8)	8 (14.8)	2.0 (2.3)
	0-24	13 (24.1)	18 (33.3)	10 (18.5)	13 (24.1)	2.0 (2.4)
	Final	13 (24.1)	18 (33.3)	10 (18.5)	13 (24.1)	2.0 (2.4)
Ziprasidone 10 mg	0-2	59 (93.7)	4 (6.3)			1.0 (1.1)
	0-4	54 (85.7)	8 (12.7)	1 (1.6)		1.0 (1.2)
	0-6	44 (69.8)	18 (28.6)	1 (1.6)		1.0 (1.3)
	0-8	40 (63.5)	21 (33.3)	2 (3.2)		1.0 (1.4)
	0-10	35 (55.6)	22 (34.9)	5 (7.9)	1 (1.6)	1.0 (1.6)
	0-12	32 (50.8)	21 (33.3)	9 (14.3)	1 (1.6)	1.0 (1.7)
	0-16	28 (44.4)	21 (33.3)	11 (17.5)	3 (4.8)	1.0 (1.8)
	0-20	24 (38.1)	21 (33.3)	10 (15.9)	8 (12.7)	1.0 (2.0)
	0-24	23 (36.5)	21 (33.3)	10 (15.9)	9 (14.3)	1.0 (2.1)
	Final	23 (36.5)	21 (33.3)	10 (15.9)	9 (14.3)	1.0 (2.1)

*Number of subjects out of total number in the study with 1, 2, 3, or 4 injections in each interval.
Source Data: Appendix V Table 6. Date of Data Extraction: 16SEP97. Date of Table Generation: 16SEP97.

Appendix 7.2.1.3 (from sponsor's submission)

Demographic Characteristics
Ziprasidone Protocol 125

	Ziprasidone 2mg			Ziprasidone 10mg		
	Male	Female	Total	Male	Female	Total
Number of Subjects	38	16	54	43	20	63
Age (years):						
18-44	31	9	40	28	17	45
45-64	5	6	11	13	3	16
> 64	2	1	3	2	0	2
Mean age (years)	36.8	41.8	38.3	40.3	39.3	40.0
Age range	18-67	24-71	18-71	20-76	22-60	20-76
Race:						
ASIAN	1	1	2	0	0	0
BLACK	11	3	14	9	7	16
OTHER	5	0	5	6	1	7
WHITE	21	12	33	28	12	40
Mean weight (kg)	84.5	83.2		85.4	79.0	
Weight range	59-127	63-104		57-123	51-113	

Source Data: APPENDIX V TABLE 2 Date of Data Extraction: 03SEP97 Date of Table Generation: 03SEP97

EFFICACY OUTCOME MEASURES FOR STUDY 125

(adapted from sponsor's electronic submission)

Study Summary of Outcomes* for Protocol 125 - All Subjects, Observed Cases

		Ziprasidone	
		2 mg	10 mg
AUC of BAS 0-2	Mean	8.30	7.57
	p-value		<0.001
	N	54	62
CGI Severity at Hour 4	Mean baseline	4.24	4.37
	Mean change	-0.74	-0.76
	% change	-17.47	-17.45
	p-value		0.870
	N	54	63
CGI Severity at Last Obs.	Mean baseline	4.24	4.37
	Mean change	-0.50	-0.71
	% change	-11.79	-16.36
	p-value		0.214
	N	54	63
AUC of BAS 0-4	Mean	15.88	13.47
	p-value		<0.001
	N	45	55
BAS Score at Hour 2 (LOCF)+	Mean baseline	4.65	4.81
	Mean change	-0.78	-1.63
	% change	-16.73	-33.89
	p-value		<0.001
	N	54	62
Responder Rate++	# responders	11	28
	% responders	21.15	45.16
	p-value		0.013
	N	52	62

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.

+BAS score at hour 2 is the the last assessment taken up to 2 hours post first injection.

++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.

**PANSS Agitation Items Score equals the sum of items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).

Source Data: Protocol 125. Date of Table Generation: 20OCT97.

Study Summary of Outcomes* for Protocol 125 - All Subjects, Observed Cases

		Ziprasidone	
		2 mg	10 mg
CGI Improvement	Mean	3.09	2.89
	p-value		0.109
	N	54	63
PANSS Total	Mean baseline	89.38	90.00
	Mean change	-12.30	-13.55
	% change	-13.76	-15.05
	p-value		0.379
	N	53	62
PANSS Agitation**	Mean baseline	14.93	15.03
	Mean change	-3.35	-4.02
	% change	-22.46	-26.72
	p-value		0.162
	N	54	62
NOSIE	Mean baseline	37.63	37.98
	Mean change	-4.28	-5.41
	% change	-11.37	-14.25
	p-value		0.349
	N	54	63

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.

+BAS score at hour 2 is the the last assessment taken up to 2 hours post first injection.

++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.

**PANSS Agitation Items Score equals the sum of items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).

Source Data: Protocol 125. Date of Table Generation: 20OCT97.

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Appendix 7.2.2.2 (from Sponsor's Submission)

Total Number of Injections by Timepoint - All Subjects, Observed Cases
Ziprasidone Protocol 126

Treatment Group	Hours Post First Dose	Number (%)* of Subjects with 1, 2, 3, or 4 Injections				Mode (Mean)
		1	2	3	4	
Ziprasidone 2 mg	0-2	38 (100.0)				1.0 (1.0)
	0-4	38 (100.0)				1.0 (1.0)
	0-6	27 (71.1)	11 (28.9)			1.0 (1.3)
	0-8	22 (57.9)	15 (39.5)	1 (2.6)		1.0 (1.4)
	0-10	19 (50.0)	14 (36.8)	5 (13.2)		1.0 (1.6)
	0-12	19 (50.0)	12 (31.6)	7 (18.4)		1.0 (1.7)
	0-16	17 (44.7)	12 (31.6)	9 (23.7)		1.0 (1.8)
	0-20	13 (34.2)	14 (36.8)	8 (21.1)	3 (7.9)	2.0 (2.0)
	0-24	10 (26.3)	16 (42.1)	8 (21.1)	4 (10.5)	2.0 (2.2)
	Final	10 (26.3)	16 (42.1)	8 (21.1)	4 (10.5)	2.0 (2.2)
Ziprasidone 20 mg	0-2	41 (100.0)				1.0 (1.0)
	0-4	41 (100.0)				1.0 (1.0)
	0-6	34 (82.9)	7 (17.1)			1.0 (1.2)
	0-8	32 (78.0)	9 (22.0)			1.0 (1.2)
	0-10	27 (65.9)	13 (31.7)	1 (2.4)		1.0 (1.4)
	0-12	27 (65.9)	13 (31.7)	3 (7.3)		1.0 (1.5)
	0-16	19 (46.3)	18 (43.9)	3 (7.3)	1 (2.4)	1.0 (1.7)
	0-20	17 (41.5)	16 (39.0)	5 (12.2)	3 (7.3)	1.0 (1.9)
	0-24	17 (41.5)	15 (36.6)	6 (14.6)	3 (7.3)	1.0 (1.9)
	Final	17 (41.5)	15 (36.6)	6 (14.6)	3 (7.3)	1.0 (1.9)

*Number of subjects out of total number in the study with 1, 2, 3, or 4 injections in each interval.
Source Data: Appendix V Table 6. Date of Data Extraction: 23SEP97. Date of Table Generation: 23SEP97.

Appendix 7.2.2.3 (from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 126

	Ziprasidone 2mg			Ziprasidone 20mg		
	Male	Female	Total	Male	Female	Total
Number of Subjects	30	8	38	32	9	41
Age (years):						
18-44	22	6	28	23	6	29
45-64	8	2	10	9	3	12
Mean age (years)	38.1	42.5	39.0	39.8	39.9	39.9
Age range	20-62	32-54	20-62	23-60	29-57	23-60
Race:						
ASIAN	1	0	1	2	0	2
BLACK	4	2	6	1	3	4
OTHER	2	0	2	4	1	5
WHITE	23	6	29	25	5	30
Mean weight (kg)	79.2	76.4		85.4	83.8	
Weight range	53-111	51-95		59-117	67-100	

Source Data: APPENDIX V TABLE 2 Date of Data Extraction: 03SEP97 Date of Table Generation: 04SEP97

EFFICACY OUTCOME MEASURES FOR STUDY 126 (adapted from sponsor's electronic submission)

Study Summary of Outcomes* for Protocol 126 - All Subjects, Observed Cases

		Ziprasidone	
		2 mg	20 mg
AUC of BAS 0-4	Mean	15.73	12.23
	p-value		<0.001
	N	38	40
CGI Severity at Hour 4	Mean baseline	4.74	4.63
	Mean change	-1.16	-1.88
	% change	-24.44	-40.54
	p-value		0.008
	N	38	40
CGI Severity at Last Obs.	Mean baseline	4.74	4.63
	Mean change	-0.92	-1.58
	% change	-19.44	-34.05
	p-value		0.004
	N	38	40
AUC of BAS 0-2	Mean	8.48	6.95
	p-value		<0.001
	N	37	40
BAS Score at Hour 4 (LOCF)+	Mean baseline	5.00	4.98
	Mean change	-1.17	-2.17
	% change	-23.42	-43.63
	p-value		<0.001
	N	38	41
Responder Rate++	# responders	10	26
	% responders	26.32	65.00
	p-value		0.001
	N	38	40

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.

+BAS score at hour 4 is the the last assessment taken up to 4 hours post first injection.

++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.

**PANSS Agitation Items Score equals the sum of items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).

Source Data: Protocol 126. Date of Table Generation: 200CT97.

Study Summary of Outcomes* for Protocol 126 - All Subjects, Observed Cases

		Ziprasidone	
		2 mg	20 mg
CGI Improvement	Mean	3.32	2.38
	p-value		<0.001
	N	38	40
PANSS Total	Mean baseline	84.00	86.66
	Mean change	-12.08	-18.30
	% change	-14.38	-21.12
	p-value		0.074
	N	38	40
PANSS Agitation**	Mean baseline	14.29	14.88
	Mean change	-4.03	-5.70
	% change	-28.18	-38.32
	p-value		0.102
	N	38	40
NOSIE	Mean baseline	34.71	35.90
	Mean change	-2.29	-4.70
	% change	-6.60	-13.09
	p-value		0.323
	N	38	40

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.

+BAS score at hour 4 is the the last assessment taken up to 4 hours post first injection.

++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.

**PANSS Agitation Items Score equals the sum of items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).

Source Data: Protocol 126. Date of Table Generation: 200CT97.

Appendix 8.1.2 Serious adverse events occurring in the extension studies in which subjects were treated with oral ziprasidone

Serious events from extension studies with oral ziprasidone

SUBJECT #	AGE/ SEX	MEAN DOSE (MG/D)	DURATION OF TREATMENT (DAYS)	SERIOUS ADVERSE EVENT/ COMMENTS
127E-5810001	43/ F		49 days	Overdose of 640 mg resulting in moderate sedation
127E-7190005	49/F	77	78	Ankle fracture
127E-7950002	65/M	77	29	Seizure
121-5810002	49/F	35	26	Erosive duodenitis
121-7550287	28/M	70	28	Dystonia
127E-5950013	34/M	137	47	Bradycardia
127E-6690008	46/M	144	43	Rib fractures, pneumothorax
127E-5950013	35/M	160	45	Bradycardia
127E-5950016	24/M	120	34	Asthma exacerbation
127E-7010003	53/M	120	6	Cardiomegaly, congestive heart failure & pneumonia
127E-7950002	65/M	40	5	Seizure with loss of consciousness
306E-3740017	26/M	80	42	Tonic clonic seizure

Appendix 8.1.5.2 (From sponsor's Electronic Submission)

Incidence Rates for Treatment-Emergent Adverse Events Reported for at Least 1% of Ziprasidone-Treated Subjects Randomized to Receive 5-20 mg per Dose
Fixed-Ziprasidone-Dose Phase II/III Studies
Intramuscular Dosing

	Ziprasidone 2mg*	Other Ziprasidone	Combined Ziprasidone	Haloperidol
Number of Subjects: Evaluable for Adverse Events	92	310	402	100
% With Adverse Events				
BODY AS A WHOLE				
ABDOMINAL PAIN		1.6	1.2	1.0
APPL/INJ/INCISION/INSERTION SITE PAIN	8.7	9.4	9.2	2.0
ASTHENIA	2.2	2.6	2.5	
HEADACHE	3.3	14.5	11.9	8.0
PAIN		1.6	1.2	2.0
CARDIOVASCULAR				
HYPERTENSION	2.2	3.9	3.5	1.0
HYPOTENSION		1.3	1.0	
POSTURAL HYPOTENSION		2.9	2.2	
TACHYCARDIA		4.8	3.7	6.0
DIGESTIVE				
CONSTIPATION		3.2	2.5	
DRY MOUTH	1.1	2.6	2.2	2.0
DYSPEPSIA	1.1	5.8	4.7	5.0
INCREASED SALIVATION		1.9	1.5	3.0
NAUSEA	4.3	14.5	12.2	3.0
VOMITING		7.7	6.0	5.0
NERVOUS				
ABNORMAL DREAMS		1.3	1.0	
AGITATION	2.2	5.8	5.0	9.0
AKATHISIA		5.5	4.2	21.0
ANXIETY	2.2	10.3	8.5	13.0
DIZZINESS	3.3	13.2	10.9	
DYSTONIA		2.9	2.2	10.0
EXTRAPYRAMIDAL SYNDROME	2.2	1.3	1.5	15.0
HYPERTONIA	1.1	1.3	1.2	11.0
INSOMNIA	3.3	10.3	8.7	12.0
SOMNOLENCE	7.6	9.4	9.0	8.0
SPEECH DISORDER		1.3	1.0	1.0
TREMOR		2.6	2.0	3.0
RESPIRATORY				
RESPIRATORY TRACT INFECTION		1.9	1.5	1.0
RHINITIS	1.1	1.6	1.5	1.0
SPECIAL SENSES				
ABNORMAL VISION		2.3	1.7	1.0

* Subjects randomized to "2mg maximum QID" group in protocols 125,126. The incidence rate in this group for adverse events occurring at the 1% level in "Other Ziprasidone" is displayed for comparison.

Only adverse events occurring in at least 1% of ziprasidone subjects in the "Other Ziprasidone" dose groups are included in this table.

Subjects with multiple occurrences of the same adverse event are counted only once for that adverse event.

Only adverse events occurring while on study treatment or within the one day after the last day of study treatment were included in this table.

Protocols: 121,125,126

Date of Table Generation: 080C19/

Appendix 8.1.5.3

(Selected from sponsor's proposed labeling)

Other Adverse Events Observed During the Premarketing Evaluation of Ziprasidone

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with ziprasidone at multiple doses > 4 mg/day within the database of 2163 patients or in additional studies of ziprasidone intramuscular at doses of \geq 5 mg (n=431). All reported events are included except those already listed in Table 1, Table 2 or elsewhere in labeling, those event terms which were so general as to be uninformative, and events reported only once and which did not have a substantial probability of being acutely life-threatening. It is important to emphasize that, although the events reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole Frequent: abdominal pain, back pain, fever, flu syndrome, headache, pain, suicidal ideation: Infrequent: abscess, accidental fall, accidental overdose, allergic reaction, cellulitis, chills, bacterial infection, face edema, fever, flu syndrome, fungal infection, infection, injection site complication, injection site reaction, intentional overdose, lab test abnormal, malaise, neoplasm, pelvic pain photosensitivity reaction, suicide attempt, suicide gesture: Rare: abdomen enlarged, hangover effect.

Cardiovascular System Frequent: hypertension, hypotension: Infrequent: angina pectoris, arrhythmia, bradycardia, electrocardiogram abnormal, hemorrhage, migraine, pallor, palpitation, syncope, vasodilation. Rare: peripheral vascular disorder, QT interval prolonged, retinal vascular disorder.

Digestive System Frequent: tooth disorder, vomiting: Infrequent: cheilitis, duodenal ulcer, dysphagia, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, gingivitis, increased appetite, liver function tests abnormal, oral moniliasis, rectal disorder, rectal hemorrhage, tongue edema, tooth caries: Rare: eructation, fecal incontinence, gum hemorrhage, stomach ulcer.

Hemic and Lymphatic System Infrequent: anemia, ecchymosis, eosinophilia, leukocytosis, leukopenia: Rare: iron deficiency anemia, thrombocytopenia.

Metabolic and Nutritional Disorders Frequent: weight gain, weight loss: Infrequent: albuminuria, dehydration, edema, hyperglycemia, peripheral edema, SGOT increased, SGPT increased, thirst: Rare: bilirubinemia, hypercholesteremia.

Musculoskeletal System Infrequent: arthrosis, bone pain, joint disorder, leg cramps, myasthenia, tenosynovitis.

Nervous System Frequent: agitation, delusions, depression, dyskinesia, hallucinations, hostility, insomnia, manic reaction, myoclonus, nervousness, paranoid reaction, paresthesia, personality disorder, psychosis, schizophrenic reaction, speech disorder, tardive dyskinesia, thinking abnormal, twitching: Infrequent: abnormal dreams, abnormal gait, akinesia, amnesia, apathy, aphasia, ataxia, catatonic reaction, choreoathetosis, cogwheel rigidity, confusion, convulsion, delirium, dementia, depersonalization, drug dependence, dysarthria, emotional lability, euphoria, grand mal convulsion, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido decreased, libido increased, neurosis, oculogyric crisis, paralysis, sleep disorder, stupor, vertigo, withdrawal syndrome: Rare: diplopia, incoordination, neuropathy, nystagmus.

Respiratory System Frequent: bronchitis, dyspnea, pharyngitis: Infrequent: asthma, epistaxis, hiccup, laryngismus, pneumonia, respiratory distress syndrome, sinusitis: Rare: pneumothorax, voice alteration.

Skin and Appendages Frequent: pruritus: Infrequent: acne, alopecia, contact dermatitis, dry

skin, furunculosis, eczema, exfoliative dermatitis, herpes simplex, maculopapular rash, psoriasis, seborrhea, skin disorder, skin hypertrophy, skin ulcer, sweating, urticaria, vesiculobullous rash. Rare: furunculosis, lichenoid dermatitis, pustular rash.

Special Senses Infrequent: blepharitis, conjunctivitis, deafness, dry eyes, ear disorder, ear pain,

eye pain, otitis externa, otitis media, retinal disorder, taste perversion, tinnitus: Rare: abnormality of accommodation, mydriasis.

Urogenital System Infrequent: abnormal ejaculation, amenorrhea, cystitis, dysmenorrhea, dysuria, gynecomastia, hematuria, impotence, leukorrhea, menorrhagia, metrorrhagia, penile erection, polyuria, urinary frequency, urinary retention, urinary tract disorder, urinary tract infection, vaginitis: Rare: anorgasmia, breast pain, kidney pain, nephritis, pyelonephritis, uterine fibroids enlarged.

Appendix 8.1.5.4 Summary tables comparisons of gender, age and race (from sponsor's ISS)

Incidence of Treatment-Emergent Adverse Events by Gender				
	2 mg Ziprasidone		Other Ziprasidone	
	Males n=68	Females n=24	Males n=259	Females n=51
Nervous	17.6	16.7	45.6	31.4
Body as a Whole	16.2	12.5	26.6	35.3
Digestive	8.8	12.5	27.4	35.3
Cardiovascular	2.9	4.2	13.1	9.8

Incidence of Treatment-Emergent Adverse Events by Age				
	2 mg Ziprasidone		Other Ziprasidone	
	18-54 years n=86	≥ 55 years n=6	18-54 years n=280	≥ 55 years n=30
Nervous	17.4	16.7	42.9	46.7
Body as a Whole	16.3	0	28.9	20.0
Digestive	9.3	16.7	28.6	30.0
Cardiovascular	2.3	16.7	12.1	16.7

Incidence of Treatment-Emergent Adverse Events by Race				
	2 mg Ziprasidone		Other Ziprasidone	
	Caucasian n=62	Black n=20	Caucasian n=207	Black n=72
Nervous	14.5	15.0	45.9	44.4
Body as a Whole	17.7	5.0	29.0	31.9
Digestive	9.7	5.0	26.1	38.9
Cardiovascular	1.6	0	11.1	13.9

Appendix 8.1.6.3.1 Median change from Baseline to Last Observation for Laboratory Test Data
All Phase II/III Studies (adapted from sponsor's submission of 12/18/97)

Laboratory Test Data: Median Change from Baseline to Last Observation
- All Phase II/III Studies - Intramuscular Dosing

GROUP	PARAMETER	UNITS	Ziprasidone 2mg**			Other Ziprasidone			Combined Ziprasidone			Haloperidol			Placebo		
			N	BASELINE MEDIAN	CHANGE FROM BASELINE	N	BASELINE MEDIAN	CHANGE FROM BASELINE	N	BASELINE MEDIAN	CHANGE FROM BASELINE	N	BASELINE MEDIAN	CHANGE FROM BASELINE	N	BASELINE MEDIAN	CHANGE FROM BASELINE
HEMATOLOGY	Hemoglobin (HGB)	G/DL	84	15	0.1	389	15	0	473	15	0	120	14.9	0.1	6	15.4	-0.1
	Hematocrit (HCT)	%	84	45	0	386	44	0	470	44	0	120	44	0	6	45	-1
	RBC Count	MILL/CMM	84	4.7	0	382	4.7	0	466	4.7	0	116	4.7	0	6	4.7	-0.1
	Platelets	THOU/CMM	80	222	7	377	222	4	457	222	4	115	214	5	6	244	14
	WBC Count	THOU/CMM	81	7.5	0.4	386	7.2	0.5	467	7.2	0.5	120	7.2	0	6	8.1	-0.2
	Eosinophils (%)	%	81	6	0	372	6	0	453	6	0	120	5	0	6	9	-1
LIVER FUNCTION	Neutrophils (abs)	THOU/CMM	81	4.96	0.45	369	4.62	0.68	450	4.73	0.56	119	4.73	0	6	4.96	-0.23
	Total Bilirubin	MG/DL	88	0.5	0	393	0.5	0	481	0.5	0	121	0.5	0	6	0.5	0.1
	Total Protein	G/DL	88	7.2	0	382	7.2	0	470	7.2	0	121	7.2	0	6	6.7	0.2
	Serum Albumin	G/DL	87	4.2	0	381	4	0	468	4	0	121	4	0	6	3.8	0.3
	Serum Globulin	G/DL	88	3.2	0	379	3.2	0	467	3.2	0	121	3.2	0	6	3	0
	SGOT(AST)	IU/L	88	24	0	394	24	0	482	24	0	121	25	12	6	35	2
	SGPT(ALT)	IU/L	88	29	1	394	29	1	482	29	1	121	28	5	6	59	14
	LDH	IU/L	88	186	1	315	179	2	403	180	2	95	179	21	6	158	8
	Alk. Phosphatase	IU/L	88	66	1	394	70	0	482	70	0	121	68	2	6	56	1
	Blood Urea Nitrogen	MG/DL	88	11	1	349	12	0	437	12	0	101	12	1	6	11	-1
ELECTROLYTES	Serum Creatinine	MG/DL	88	1	0	394	1	0	482	1	0	121	1	0	6	0.9	0
	Uric Acid	MG/DL	88	5.8	-0.3	317	5.8	-0.2	405	5.8	-0.3	95	5.8	-0.1	6	5	0
	Sodium	MEQ/L	88	140	0	392	140	0	480	140	0	121	140	0	6	138	1
	Potassium	MEQ/L	88	4.3	0	390	4.3	0	478	4.3	0	121	4.2	0	6	4.2	-0.1
	Chloride	MEQ/L	88	102	0	393	102	-1	481	102	-1	121	102	0	6	102	1
	Calcium	MG/DL	88	9.4	0	393	9.4	0	481	9.4	0	121	9.4	0	6	9.3	-0.2
LIPIDS	Phosphorus	MG/DL	88	4.1	0.1	380	3.7	0.1	468	3.8	0.1	121	3.8	0	6	3.8	0.3
	Glucose, Random	MG/DL	88	84	2	380	87	1	468	86	1	121	86	3	6	101	4
	Cholesterol	MG/DL	88	159	6	316	159	1	404	159	2	95	163	0	6	168	16
	Triglycerides	MG/DL	88	130	11	316	129	10	404	129	10	95	116	5	6	140	8
URINE	Specific Gravity		88	1.018	0	312	1.02	0	400	1.02	0	94	1.02	0	6	1.018	0.002
	Urine pH		87	5	0	314	5	0	401	5	0	94	5	0	6	5	0
	Protein (qual)		70	0	0	101	0	0	171	0	0		0	0	6	0	0
	Protein (quant)	MG/DAY	.	.	.	1	26.4	460.1	1	26.4	460.1
	Urine Glucose		1	20	0	.	.	.

Based on Laboratory Test Results:

1. Converted to Standard Reporting Units

2. Adjusted to a Common Set Upper and Lower Reference Limits

** Subjects randomized to '2mg maximum QID' in protocols 125,126

N = Total number of subjects with at least one observation of the given lab parameter while on study treatment or the one day after the last day of study treatment were included in this table.

Includes protocols 046, 120, 121, 125, 126, 127E, 306, 306E

Date of Table Generation: 15OCT97

Appendix 8.1.6.3.2a Sponsor's Laboratory Reference Ranges to Determine Baseline Abnormality
(from sponsor's submission 12/18/97)

1.2 Pfizer-Defined External Reference Ranges for Normalization of Laboratory Test Data			
Clinical Laboratory Test	Standard Units	Reference Range	
		LLN	ULN
Hemoglobin	G/DL	13.800	17.20
Hematocrit	%	41.000	50.00
Red Blood Cells	MILL/CMM	4.400	5.80
Platelets	THOU/CMM	130.000	400.00
White Blood Cells	THOU/CMM	3.800	10.80
Eosinophils (%)	%	0.000	7.00
Erythrocyte Sedimentation Rate	MM/H	0.000	15.00
Prothrombin Time Quick	SEC	10.900	12.70
Total Bilirubin	MG/DL	0.000	1.30
Direct Bilirubin	MG/DL	0.000	0.40
Protein (total)	G/DL	6.000	8.50
Albumin	G/DL	3.200	5.00
Globulin	G/DL	2.200	4.20
Aspartate Aminotransferase (GOT)	IU/L	0.000	42.00
Alanine Aminotransferase (GPT)	IU/L	0.000	48.00
Lactate Dehydrogenase	IU/L	0.000	250.00
Alkaline Phosphatase	IU/L	20.000	125.00
Blood Urea Nitrogen	MG/DL	7.000	25.00
Creatinine	MG/DL	0.700	1.40
Urate	MG/DL	4.000	8.50
Sodium	MEQ/L	135.000	146.00
Potassium	MEQ/L	3.500	5.30
Chloride	MEQ/L	95.000	108.00
Bicarbonate	MEQ/L	19.000	31.00
Calcium	MG/DL	8.500	10.30
Phosphate	MG/DL	2.500	4.50
Cholesterol	MG/DL	0.000	200.00
Triglycerides	MG/DL	0.000	200.00
Glucose (fasting)	MG/DL	70.000	115.00
Glucose (random)	MG/DL	70.000	115.00
Urine Specific Gravity		1.001	1.04
Urine pH		4.600	8.00
Urine Protein		0.000	0.00
Urine Glucose		0.000	0.00
Urine WBC	/HPF	0.000	5.00
Urine RBC	/HPF	0.000	3.00
Urine Ketones		0.000	0.00
Urine Granular Casts	/LPF	0.000	0.00
Urine Hyaline Casts	/LPF	0.000	0.00
Urine Bilirubin		0.000	0.00
Cholesterol (LDL)	MG/DL	0.000	129.00
Cholesterol (HDL)	MG/DL	45.000	999.00
Thyroxine (T4)	MCG/DL	4.500	12.50
Magnesium	MG/DL	1.700	2.50
Prolactin	NG/ML	0.000	20.00
Urine Calcium	MG/DAY	50.000	400.00
Urine Glucose (24 Hr) Quantitative	MG/DAY	0.000	300.00
Urine (24hr) Protein	MG/DAY	25.000	75.00
TSH	MCIU/ML	0.400	5.50
Urine WBC Cast	/LPF	0.000	0.00
Urine (24 hr) Creatinine	MG/DAY	800.000	2400.00
Urine RBC Casts	/LPF	0.000	0.00
Neutrophils (Abs)	THOU/CMM	1.800	8.00

Appendix 8.1.6.3.2b Incidence of clinically significant laboratory abnormalities for all ziprasidone IM Phase II/III studies (extracted from review of Pfizer's NDA 20-825 for ziprasidone po).

					Column "A"	Column "B"
Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Post-baseline Clin Sig Criterion for BL abnormal (Tier 2)
1	Hemoglobin (HGB)	G/DL	HEMATOLOGY	> 1.0 x ULN	>20% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>20% Decrease from baseline	< 90% of baseline
2	Hematocrit (HCT)	%	HEMATOLOGY	> 1.0 x ULN	>20% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>20% Decrease from baseline	< 90% of baseline
3	RBC Count	MILL/CMM	HEMATOLOGY	> 1.0 x ULN	>25% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>25% Decrease from baseline	< 90% of baseline
5	Platelets	THOU/CMM	HEMATOLOGY	> 1.0 x ULN	> 700	> 120% of baseline
				< 1.0 x LLN	< 75	< 80% of baseline
7	WBC Count	THOU/CMM	HEMATOLOGY	> 1.0 x ULN	> 17.5	> 125% of baseline
				< 1.0 x LLN	< 2.5	< 75% of baseline
14	ESR	MM/H	HEMATOLOGY	> 1.0 x ULN (x)	> 1.2 x ULN	> 120% of baseline
19	Prothrombin Time	SEC	HEMATOLOGY	> 1.0 x ULN	> 1.2 x ULN	> 120% of baseline
608	Neutrophils (abs)	THOU/CMM	HEMATOLOGY	< 1.0 x ULN	< 1.0	< 75% of baseline
9	Eosinophils (%)	%	HEMATOLOGY	> 1.0 x ULN	>= 10%	> 150% of baseline
21	Total Bilirubin	MG/DL	LIVER FUNCTION	> 1.0 x ULN (x)	> 1.5 x ULN	> 150% of baseline
22	Direct Bilirubin	MG/DL	LIVER FUNCTION	> 1.0 x ULN (x)	> 1.5 x ULN	> 150% of baseline
24	Total Protein	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	0.9 < x LLN	< 90% of baseline
25	Serum Albumin	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.1 x ULN	> 120% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 80% of baseline
26	Serum Globulin	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.2 x ULN	> 150% of baseline
				< 1.0 x LLN	< 0.8 x LLN	< 50% of baseline

Appendix 8.1.6.3.2b (con't) Incidence of clinically significant laboratory abnormalities for all ziprasidone IM Phase II/III studies (extracted from review of Pfizer's NDA 20-825 for ziprasidone po).

Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Column "A"	Column "B"
					Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Post-baseline Clin Sig Criterion for BL abnormal (Tier 2)
28	SGOT(AST)	IU/L	LIVER FUNCTION	>1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
30	SGPT(ALT)	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
32	LDH	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
35	Alkaline Phosphatase	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 150% of baseline
47	BUN	MG/DL	RENAL FUNCTION	> 1.0 x ULN (x)	> 1.3 x ULN	> 130% of baseline
48	Creatinine	MG/DL	RENAL FUNCTION	> 1.0 x ULN (x)	> 1.3 x ULN	> 130% of baseline
54	Sodium	MEQ/L	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.05 x ULN < 0.95 x LLN	> 105% of baseline < 95% of baseline
55	Potassium	MEQ/L	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.1 x ULN < 0.9 x LLN	> 110% of baseline < 90% of baseline
56	Chloride	MEQ/L	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.1 x ULN < 0.9 x LLN	> 110% of baseline < 90% of baseline
57	Bicarbonate	MEQ/L	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.1 x ULN < 0.9 x LLN	> 110% of baseline < 90% of baseline
58	Calcium	MG/DL	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.1 x ULN < 0.9 x LLN	> 110% of baseline < 90% of baseline
59	Phosphorus	MG/DL	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.2 x ULN < 0.8 x LLN	> 120% of baseline < 80% of baseline
50	Uric Acid	MG/DL	ELECTROLYTES	> 1.0 x ULN	> 1.2 x ULN	> 120% of baseline
199	Magnesium	MEQ/L	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.1 x ULN < 0.9 x LLN	> 110% of baseline < 90% of baseline
63	Cholesterol	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 150% of baseline
173	HDL Cholesterol	MG/DL	LIPIDS	< 1.0 x LLN (?)	< 0.8 x LLN	< 80% of baseline
172	LDL Cholesterol	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 120% of baseline
64	Triglycerides	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 150% of baseline
67	Glucose, Fasting	MG/DL		> 1.0 x ULN < 1.0 x LLN	> 1.2 x ULN < 0.6 x LLN	> 150% of baseline < 50% of baseline
223	Prolactin	NG/ML		> 1.0 x ULN (x)	> 1.1 x ULN	> 150% of baseline

Appendix 8.1.6.3.2b (con't) Incidence of clinically significant laboratory abnormalities for all ziprasidone IM Phase II/III studies (extracted from review of Pfizer's NDA 20-825 for ziprasidone po).

Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Column "A"	Column "B"
					Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Post-baseline Clin Sig Criterion for BL abnormal (Tier 2)
78	Protein (qual)		URINE	> 1.0 x ULN	≥ 2+	> baseline + 2
79	Urine Glucose		URINE	> 1.0 x ULN	≥ 2+	> baseline + 2
80	Urine WBC	/HPF	URINE	> 1.0 x ULN	≥ 6	> baseline + 6
81	Urine RBC	/HPF	URINE	> 1.0 x ULN	≥ 6	> baseline + 6
86	Ketones (qual)		URINE	> 1.0 x ULN	≥ 1+	> baseline + 1
88	Granular Casts	/LPF	URINE	> 1.0 x ULN	> 1	> baseline + 1
90	Hyaline Casts	/LPF	URINE	> 1.0 x ULN	> 1	> baseline + 1
115	Bilirubin (qual)		URINE	> 1.0 x ULN	≥ 1+	> baseline + 1
600	Red Cell Cast	/LPF	URINE	> 1.0 x ULN	≥ 1	> baseline + 1
442	White Cell Cast	/LPF	URINE	> 1.0 x ULN	≥ 1	> baseline + 1
76	Specific Gravity		URINE	> 1.0 x ULN	> 1.035	> 1.035
				< 1.0 x LLN	< 1.000	< 1.000
77	Urine pH		URINE	> 1.0 x ULN	> 1.1 x ULN	> 1.1 x ULN
				< 1.0 x LLN	< 0.9 x LLN	< 0.9 x LLN
495	Creatinine	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
302	Calcium (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
308	Protein (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
307	Glucose (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline

Appendix 8.1.6.3.2c Incident of Clinically Significant Laboratory Test in all oral Phase II/III Studies
(adapted from sponsor's submission 12/18/98)

Incidence of Clinically Significant Laboratory Test Abnormalities
- All Phase II/III Studies - Intramuscular Dosing Tier 2 - Adjusted for Abnormal Baseline

Number of Subjects: Evaluable for laboratory abnormalities With Clinically significant laboratory abnormalities				Ziprasidone 2mg** 90 14 (16%)			Other Ziprasidone 403 78 (19%)			Combined Ziprasidone 493 92 (19%)		
				Subjects with Abnormalities			Subjects with Abnormalities			Subjects with Abnormalities		
Group	Parameter	Units	Criteria*	N	n	%	N	n	%	N	n	%
HEMATOLOGY	Hemoglobin (HGB)	G/DL	> 20% decrease*	88	0	0	401	0	0	489	0	0
	Hematocrit (HCT)	%	> 20% decrease*	88	0	0	401	0	0	489	0	0
	RBC Count	MILL/CMH	> 25% decrease*	88	0	0	401	0	0	489	0	0
	Platelets	THOU/CMH	> 75	88	0	0	394	0	0	482	0	0
	WBC Count	THOU/CMH	> 700	88	0	0	394	0	0	482	0	0
			< 2.5	88	0	0	401	0	0	489	0	0
			> 17.5	88	0	0	401	1	0	489	1	0
	Eosinophils (%)	%	> 10%	88	2	2	401	6	1	489	8	2
	Neutrophils (abs)	THOU/CMH	< 1.0	88	0	0	401	0	0	489	0	0
	Total Bilirubin	MG/DL	> 1.5 x ULN	90	0	0	402	1	0	492	1	0
LIVER FUNCTION	Total Protein	G/DL	< 0.9 x LLN	90	0	0	391	0	0	481	0	0
			> 1.1 x ULN	90	0	0	391	0	0	481	0	0
	Serum Albumin	G/DL	< 0.9 x LLN	90	0	0	390	0	0	480	0	0
			> 1.1 x ULN	90	0	0	390	1	0	480	1	0
	Serum Globulin	G/DL	< 0.8 x LLN	90	0	0	389	0	0	479	0	0
			> 1.2 x ULN	90	0	0	389	0	0	479	0	0
	SGOT(AST)	IU/L	> 3.0 x ULN	90	1	1	403	0	0	493	1	0
	SGPT(ALT)	IU/L	> 3.0 x ULN	90	0	0	403	0	0	493	0	0
	LDH	IU/L	> 3.0 x ULN	90	0	0	317	1	0	407	1	0
	Alk. Phosphatase	IU/L	> 3.0 x ULN	90	0	0	403	0	0	493	0	0
RENAL FUNCTION	Direct Bilirubin	MG/DL	> 1.5 x ULN									
	Blood Urea Nitrogen	MG/DL	> 1.3 x ULN									
	Serum Creatinine	MG/DL	> 1.3 x ULN	90	0	0	351	0	0	441	0	0
ELECTROLYTES	Uric Acid	MG/DL	> 1.2 x ULN	90	0	0	403	0	0	493	0	0
	Sodium	MEQ/L	< 0.95 x LLN	90	0	0	319	0	0	409	0	0
			> 1.05 x ULN	90	0	0	402	0	0	492	0	0
	Potassium	MEQ/L	< 0.9 x LLN	90	0	0	402	0	0	492	0	0
			> 1.1 x ULN	90	1	1	402	5	1	492	6	1
	Chloride	MEQ/L	< 0.9 x LLN	90	0	0	402	0	0	492	0	0
			> 1.1 x ULN	90	0	0	402	0	0	492	0	0
	Calcium	MG/DL	< 0.9 x LLN	90	0	0	402	0	0	492	0	0
			> 1.1 x ULN	90	0	0	402	0	0	492	0	0
	Phosphorus	MG/DL	< 0.8 x LLN	90	0	0	389	2	1	479	2	0
	Glucose, Random	MG/DL	> 1.2 x ULN	90	1	1	389	6	2	479	7	1
			< 0.6 x LLN	90	0	0	402	9	2	492	9	2
	Bicarbonate	MEQ/L	< 0.6 x LLN	90	0	0	402	6	1	492	6	1
			> 1.1 x ULN				2	0	0	2	0	0
							2	0	0	2	0	0
ELECTROLYTES	Glucose, Fasting	MG/DL	> 1.2 x ULN				1	0	0	1	0	0
			< 0.6 x LLN				1	0	0	1	0	0
LIPIDS	Cholesterol	MG/DL	> 1.2 x ULN	90	1	1	318	0	0	408	1	0
	Triglycerides	MG/DL	> 1.2 x ULN	90	4	4	318	24	8	408	28	7
URINE	Specific Gravity		< 1.000	90	0	0	315	0	0	405	0	0
			> 1.035	90	0	0	315	0	0	405	0	0
	Urine pH		< 0.9 x LLN	90	0	0	316	0	0	406	0	0
			> 1.1 x ULN	90	0	0	316	1	0	406	1	0
	Protein (qual)		> 2+	90	0	0	334	0	0	424	0	0
	Urine Glucose		> 2+	90	1	1	323	8	2	413	9	2
	Urine WBC	/HPF	> 6	90	5	6	306	12	4	396	17	4
	Urine RBC	/HPF	> 6	90	2	2	312	6	2	402	8	2
	Ketones (qual)		> 1+	90	0	0	322	2	1	412	2	0
	Bilirubin (qual)		> 1+	1	0	0	1	0	0	2	0	0
HORMONES	Protein (quant)	MG/DAY	> 1.1 x ULN				4	1	25	4	1	25
	White Cell Cast	/LPF	> 1				1	0	0	1	0	0
	TSH	MCIU/ML	< 0.8 x LLN	52	0	0	54	0	0	116	0	0
			> 1.2 x ULN	52	0	0	54	0	0	116	0	0

Includes protocols 046, 120, 121, 125, 126, 127E, 306, 306E

** Subjects randomized to 2mg maximum QID in protocols 125,126

N = Total number of subjects with at least one observation of the given lab parameter while on study treatment or the one day after the last day of study treatment were included in this table.

n = Number of subjects with a clinically significant abnormality

* Change from baseline

Date of Table Generation: 15OCT97

Appendix 8.1.6.3.2c (con't) Incident of Clinically Significant Laboratory Test in all oral Phase II/III Studies (adapted from sponsor's submission 12/18/98)

Incidence of Clinically Significant Laboratory Test Abnormalities
- All Phase II/III Studies - Intramuscular Dosing Tier 2 - Adjusted for Abnormal Baseline

Number of Subjects: Evaluable for laboratory abnormalities With Clinically significant laboratory abnormalities				Haloperidol 125 19 (15%)			Placebo 6 1 (17%)		
				Subjects with Abnormalities			Subjects with Abnormalities		
Group	Parameter	Units	Criteria*	N	n	%	N	n	%
HEMATOLOGY	Hemoglobin (HGB)	G/DL	> 20% decrease*	125	0	0	6	0	0
	Hematocrit (HCT)	%	> 20% decrease*	125	0	0	6	0	0
	RBC Count	MILL/CMM	> 25% decrease*	124	0	0	6	0	0
	Platelets	THOU/CMM	< 75	121	0	0	6	0	0
	WBC Count	THOU/CMM	> 700	121	0	0	6	0	0
LIVER FUNCTION			< 2.5	125	0	0	6	0	0
			> 17.5	125	0	0	6	0	0
	Eosinophils (%)	%	>= 10%	125	0	0	6	0	0
	Neutrophils (abs)	THOU/CMM	< 1.0	125	0	0	6	0	0
	Total Bilirubin	MG/DL	> 1.5 x ULN	125	0	0	6	0	0
	Total Protein	G/DL	< 0.9 x LLN	125	0	0	6	0	0
			> 1.1 x ULN	125	0	0	6	0	0
	Serum Albumin	G/DL	< 0.9 x LLN	125	0	0	6	0	0
			> 1.1 x ULN	125	0	0	6	0	0
	Serum Globulin	G/DL	< 0.8 x LLN	125	0	0	6	0	0
RENAL FUNCTION			> 1.2 x ULN	125	0	0	6	0	0
	SGOT(AST)	IU/L	> 3.0 x ULN	125	3	2	6	0	0
	SGPT(ALT)	IU/L	> 3.0 x ULN	125	0	0	6	0	0
	LDH	IU/L	> 3.0 x ULN	95	0	0	6	0	0
	Alk. Phosphatase	IU/L	> 3.0 x ULN	125	0	0	6	0	0
	Direct Bilirubin	MG/DL	> 1.5 x ULN				1	0	0
	Blood Urea Nitrogen	MG/DL	> 1.3 x ULN	101	0	0	6	0	0
	Serum Creatinine	MG/DL	> 1.3 x ULN	125	0	0	6	0	0
	Uric Acid	MG/DL	> 1.2 x ULN	95	0	0	6	0	0
	Sodium	MEQ/L	< 0.95 x LLN	125	0	0	6	0	0
ELECTROLYTES			> 1.05 x ULN	125	0	0	6	0	0
	Potassium	MEQ/L	< 0.9 x LLN	125	0	0	6	0	0
			> 1.1 x ULN	125	1	1	6	0	0
	Chloride	MEQ/L	< 0.9 x LLN	125	0	0	6	0	0
			> 1.1 x ULN	125	0	0	6	0	0
	Calcium	MG/DL	< 0.9 x LLN	125	0	0	6	0	0
			> 1.1 x ULN	125	0	0	6	0	0
	Phosphorus	MG/DL	< 0.8 x LLN	125	0	0	6	0	0
			> 1.2 x ULN	125	3	2	6	0	0
	Glucose, Random	MG/DL	> 1.2 x ULN	125	0	0	6	0	0
ELECTROLYTES			< 0.6 x LLN	125	1	1	6	0	0
	Bicarbonate	MEQ/L	< 0.9 x LLN	1	0	0			
			> 1.1 x ULN	1	0	0			
	Glucose, Fasting	MG/DL	> 1.2 x ULN						
			< 0.6 x LLN						
	Cholesterol	MG/DL	> 1.2 x ULN	95	0	0	6	0	0
	Triglycerides	MG/DL	> 1.2 x ULN	95	3	3	6	1	17
	Specific Gravity		< 1.000	95	0	0	6	0	0
			> 1.035	95	0	0	6	0	0
	Urine pH		< 0.9 x LLN	95	0	0	6	0	0
URINE			> 1.1 x ULN	95	0	0	6	0	0
	Protein (qual)		>= 2+	99	0	0	6	0	0
	Urine Glucose		>= 2+	99	3	3	6	0	0
	Urine WBC	/HPF	>= 6	94	7	7	3	0	0
	Urine RBC	/HPF	>= 6	97	0	0			
	Ketones (qual)		>= 1+	99	0	0	6	0	0
	Bilirubin (qual)		>= 1+						
	Protein (quant)	MG/DAY	> 1.1 x ULN						
	White Cell Cast	/LPF	>= 1						
	TSH	MCIU/ML	< 0.8 x LLN						
HORMONES			> 1.2 x ULN						

Includes protocols 046, 120, 121, 125, 126, 127E, 306, 306E

** Subjects randomized to '2mg maximum QID' in protocols 125, 126

N = Total number of subjects with at least one observation of the given lab parameter while on study treatment or the one day after the last day of study treatment were included in this table.

n = Number of subjects with a clinically significant abnormality

* Change from baseline

Appendix 8.1.6.4 Incidence of Clinically Significant Renal Laboratory Results taken during days 1-4 of Study 121 (adapted from sponsor's submission)

Incidence of Clinically Significant Renal Laboratory Results
Protocol 121
Day Category=Patients Abnormal Anytime During Day 1-4

		Ziprasidone 5mg			Ziprasidone 10mg			Ziprasidone 20mg			All Ziprasidone			Haloperidol		
		N	Total Abn.	%	N	Total Abn.	%	N	Total Abn.	%	N	Total Abn.	%	N	Total Abn.	%
Test	Criteria															
U. Microalbumin	>=20 mg/L	65	6	9.2	67	2	3.0	64	4	6.3	196	12	6.1	95	9	9.5
U. NAG:creat ratio	>1.0 U/mmol	65	5	7.7	67	2	3.0	64	4	6.3	196	11	5.6	95	3	3.2
U. Total Protein	>=0.1 g/L	65	1	1.5	67	4	6.0	64	3	4.7	196	8	4.1	95	5	5.3
U. B2-Microglobulin	>=0.3 mg/L	65	0	0	67	0	0	64	0	0	196	0	0	95	0	0
At Least One Test		65	10	15.4	67	5	7.5	64	6	9.4	196	21	10.7	95	12	12.6
Two or More Tests		65	1	1.5	67	2	3.0	64	4	6.3	196	7	3.6	95	4	4.2

Total Changed = number of subjects with an renal reading meeting criteria while on study treatment or within six days after the last day of study treatment (IM or oral).

Source Data: Appendix V - Table 8 Date of table generation: 14OCT97.

Appendix 8.1.7.3.1 Study 046 Mean changes in standing and supine systolic blood pressure, heart rate, and QTc, comparing changes from baseline (sponsor's submission 10/19/98)

Mean QTc, Standing and Supine Systolic Blood Pressure and Heart Rate, at Baseline and Changes at Day 2 and Day 4
Ziprasidone Protocol 128-046 13:08 Monday, October 19, 1998

Treatment	Baseline (Raw Values)										Day 2 - -1 Hour Post Dose (Changes from Baseline)									
	QTc (msec)		Standing Heart Rate (bpm)		Standing Systolic (mmHg)		Supine Heart Rate (bpm)		Supine Systolic (mmHg)		QTc (msec)		Standing Heart Rate (bpm)		Standing Systolic (mmHg)		Supine Heart Rate (bpm)		Supine Systolic (mmHg)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
20 mg	404	11.3	77	11.1	111	10.6	75	10.0	116	10.3	4	20.4	13	8.2	3	11.2	7	7.6	-3	12.2
40 mg	395	16.4	90	14.4	127	15.3	79	14.1	127	13.4	11	13.2	11	6.9	5	15.7	8	7.8	2	18.9
80 mg	400	16.6	94	7.4	127	23.4	84	7.0	128	18.4	13	9.8	8	15.2	5	13.5	0	14.7	-3	12.7
Placebo	399	11.4	85	10.7	126	5.1	79	9.4	126	8.7	5	18.4	13	17.4	1	7.1	6	8.3	-5	11.8

(CONTINUED)

Treatment	Day 4 - -17 Hours Post Dose (Changes from Baseline)									
	QTc (msec)		Standing Heart Rate (bpm)		Standing Systolic (mmHg)		Supine Heart Rate (bpm)		Supine Systolic (mmHg)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
20 mg	-4	20.3	19	9.0	10	10.5	5	11.7	8	13.6
40 mg	22	15.3	14	13.8	4	9.8	6	11.9	-1	14.2
80 mg	19	7.3	9	13.5	3	19.4	1	10.7	2	15.8
Placebo	1	11.8	1	13.4	-10	7.7	-5	4.3	-6	7.0

Clinically significant vitals from study 046 (from sponsor's submission 12/18/97)

Vital Signs: Incidence of Clinically Significant Changes from Baseline
Ziprasidone Protocol 046

	Ziprasidone 20mg/day			Ziprasidone 40mg/day			Ziprasidone 80mg/day			Placebo		
	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed
Standing Systolic BP (mmHg)												
Increase (BP>180, CHG>=20)	6	0	0.0	7	0	0.0	6	0	0.0	6	0	0.0
Decrease (BP<90, CHG<=-20)	6	0	0.0	7	0	0.0	6	0	0.0	6	1	16.7
Standing Diastolic BP (mmHg)												
Increase (BP>105, CHG>=15)	6	0	0.0	7	0	0.0	6	0	0.0	6	1	16.7
Decrease (BP<50, CHG<=-15)	6	0	0.0	7	0	0.0	6	0	0.0	6	0	0.0
Standing Heart Rate (bpm)												
Increase (HR>120, CHG>=15)	6	2	33.3	7	4	57.1	6	1	16.7	6	1	16.7
Decrease (HR<50, CHG<=-15)	6	0	0.0	7	0	0.0	6	0	0.0	6	0	0.0
Supine Systolic BP (mmHg)												
Increase (BP>180, CHG>=20)	6	0	0.0	7	0	0.0	6	0	0.0	6	0	0.0
Decrease (BP<90, CHG<=-20)	6	0	0.0	7	0	0.0	6	0	0.0	6	0	0.0
Supine Diastolic BP (mmHg)												
Increase (BP>105, CHG>=15)	6	0	0.0	7	0	0.0	6	0	0.0	6	0	0.0
Decrease (BP<50, CHG<=-15)	6	0	0.0	7	0	0.0	6	0	0.0	6	0	0.0
Supine Heart Rate (bpm)												
Increase (HR>120, CHG>=15)	6	0	0.0	7	1	14.3	6	0	0.0	6	0	0.0
Decrease (HR<50, CHG<=-15)	6	0	0.0	7	0	0.0	6	0	0.0	6	0	0.0

N is the total number of subjects with a baseline observation and at least one observation while on study drug or within 1 day of the day of dosing for the given vital sign parameter.

Source Data: Appendix V Table 9

Date of Data Extraction: 07AUG97

Date of Table Generation: 13AUG97

Appendix 8.1.7.3.2 Incidence of clinically significant changes in vital signs in the integrated safety data base. (from sponsor's submission: 12/18/97)

	Ziprasidone 2mg*			Other Ziprasidone			Combined Ziprasidone			Haloperidol			Placebo		
	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed
Standing Systolic BP (mmHg)															
Increase (BP>180, CHG<=-20)	90	0	0.0	412	5	1.2	502	5	1.0	131	3	2.3	6	0	0.0
Decrease (BP<90, CHG<=-20)	90	2	2.2	412	28	6.8	502	30	6.0	131	8	6.1	6	1	16.7
Standing Diastolic BP (mmHg)															
Increase (BP>105, CHG<=-15)	90	2	2.2	412	30	7.3	502	32	6.4	131	4	3.1	6	1	16.7
Decrease (BP<50, CHG<=-15)	90	0	0.0	412	9	2.2	502	9	1.8	131	3	2.3	6	0	0.0
Standing Heart Rate (bpm)															
Increase (HR>120, CHG<=-15)	89	2	2.2	412	76	18.4	501	78	15.6	131	17	13.0	6	1	16.7
Decrease (HR<50, CHG<=-15)	89	0	0.0	412	1	0.2	501	1	0.2	131	0	0.0	6	0	0.0
Sitting Systolic BP (mmHg)															
Increase (BP>180, CHG<=-20)	92	1	1.1	400	3	0.8	492	4	0.8	133	1	0.8	0	0	
Decrease (BP<90, CHG<=-20)	92	1	1.1	400	15	3.8	492	16	3.3	133	4	3.0	0	0	
Sitting Diastolic BP (mmHg)															
Increase (BP>105, CHG<=-15)	92	0	0.0	400	23	5.8	492	23	4.7	133	7	5.3	0	0	
Decrease (BP<50, CHG<=-15)	92	0	0.0	400	8	2.0	492	8	1.6	133	3	2.3	0	0	
Sitting Heart Rate (bpm)															
Increase (HR>120, CHG<=-15)	92	0	0.0	400	24	6.0	492	24	4.9	133	10	7.5	0	0	
Decrease (HR<50, CHG<=-15)	92	0	0.0	400	2	0.5	492	2	0.4	133	0	0.0	0	0	
Supine Systolic BP (mmHg)															
Increase (BP>180, CHG<=-20)	0	0		19	0	0.0	19	0	0.0	0	0		6	0	0.0
Decrease (BP<90, CHG<=-20)	0	0		19	0	0.0	19	0	0.0	0	0		6	0	0.0
Supine Diastolic BP (mmHg)															
Increase (BP>105, CHG<=-15)	0	0		19	0	0.0	19	0	0.0	0	0		6	0	0.0
Decrease (BP<50, CHG<=-15)	0	0		19	0	0.0	19	0	0.0	0	0		6	0	0.0
Supine Heart Rate (bpm)															
Increase (HR>120, CHG<=-15)	0	0		19	1	5.3	19	1	5.3	0	0		6	0	0.0
Decrease (HR<50, CHG<=-15)	0	0		19	0	0.0	19	0	0.0	0	0		6	0	0.0
Weight (kg)															
Increase (CHG>=7%)	27	0	0.0	55	0	0.0	82	0	0.0	7	0	0.0	0	0	
Decrease (CHG<=-7%)	27	0	0.0	55	0	0.0	82	0	0.0	7	0	0.0	0	0	

* Subjects randomized to "2mg maximum O10" group in protocols 125,126
N is the total number of subjects with a baseline observation and at least one observation while on study treatment or within one day after the last day of study treatment for the given vital sign parameter.
To be a clinically significant change, a value has to both meet the criterion value and represent a change from baseline of at least the magnitude noted at any time during the study treatment or within the one day after the study treatment.
Protocols: 046,120,121,125,126,127F,306,306E
Date of Table Generation: 09OCT97

Appendix 8.1.8.3a Study 046: Mean change from baseline to ECG Reading one hour (approximately tmax) after the fourth dose on day 2

Change from Baseline to ECG Reading following Fourth IM Dose on Day 2 Protocol 046 - Central Reader Data									
Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc int (msec)	20mg/day	6	404.3	404.5	389-418	407.8	411.0	369-437	3.5
	40mg/day	6	395.3	386.5	380-422	406.3	404.0	388-436	11.0
	80mg/day	6	399.5	401.0	375-422	412.0	410.5	380-440	12.5
	Placebo	6	398.7	396.0	385-413	404.0	402.5	382-424	5.3
QT int (msec)	20mg/day	6	352.8	352.0	311-395	344.8	346.0	291-388	-8.0
	40mg/day	6	339.3	336.5	295-390	333.5	336.5	286-373	-5.8
	80mg/day	6	337.0	336.5	328-347	345.3	345.5	322-379	8.3
	Placebo	6	341.3	339.0	321-370	343.0	339.5	324-381	1.7
Heart Rate (bpm)	20mg/day	6	79.8	77.5	66-94	84.7	82.5	76-97	4.8
	40mg/day	6	84.0	82.5	58-123	91.7	85.0	68-140	7.7
	80mg/day	6	84.5	84.0	77-94	86.0	82.5	78-106	1.5
	Placebo	6	82.0	81.5	74-89	84.0	87.5	67-92	2.0
PR int (msec)	20mg/day	6	139.0	136.5	123-165	137.3	136.0	124-157	-1.7
	40mg/day	6	153.5	154.5	126-176	138.2	139.0	124-150	-15.3
	80mg/day	6	152.5	154.5	136-168	147.0	148.0	123-165	-5.5
	Placebo	6	165.0	165.5	142-190	160.7	160.5	136-180	-4.3
QRS int (msec)	20mg/day	6	89.0	87.0	80-100	88.0	86.0	80-102	-1.0
	40mg/day	6	86.2	85.0	79-98	86.7	85.0	81-94	0.5
	80mg/day	6	89.0	88.5	85-94	91.3	93.0	82-96	2.3
	Placebo	6	88.5	88.0	81-97	90.0	89.5	82-101	1.5

*QTc int = QT int/SQRT(60/(Heart Rate))
 Baseline = last ECG taken before the first day of study treatment.
 Final = last ECG taken while on study treatment or within one day after the last day of study treatment.
 Subj. 05570021 (40mg/day) withdrew following the 2nd injection on Day 1 and is not included in this summary.
 Source Data: Appendix V, Table 10 Date of Data Extraction: 24OCT97 Date of table generation: 05NOV97

Study 046: Change from baseline to last observation (approx. 18 hours after last dose of IM ziprasidone)

Change from Baseline to Last Observation in ECG Readings
Protocol 046 - Central Read Data

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc int (msec)	20mg/day	6	404.3	404.5	389-418	400.8	406.0	371-429	-3.5
	40mg/day	7	395.1	389.0	380-422	419.0	427.0	394-431	23.9
	80mg/day	6	399.5	401.0	375-422	418.0	418.5	405-430	18.5
	Placebo	6	398.7	396.0	385-413	399.5	401.5	389-406	0.8
QT int (msec)	20mg/day	6	352.8	352.0	311-395	347.2	354.5	305-370	-5.7
	40mg/day	7	336.6	327.0	295-390	335.1	337.0	292-380	-1.4
	80mg/day	6	337.0	336.5	328-347	341.5	335.0	321-380	4.5
	Placebo	6	341.3	339.0	321-370	354.0	359.5	322-369	12.7
Heart Rate (bpm)	20mg/day	6	79.8	77.5	66-94	80.3	79.5	74-89	0.5
	40mg/day	7	85.0	83.0	58-123	96.3	88.0	71-131	11.3
	80mg/day	6	84.5	84.0	77-94	90.5	93.0	77-98	6.0
	Placebo	6	82.0	81.5	74-89	76.8	75.5	72-88	-5.2
PR int (msec)	20mg/day	6	139.0	136.5	123-165	137.0	132.5	124-160	-2.0
	40mg/day	7	152.3	153.0	126-176	146.3	146.0	131-167	-6.0
	80mg/day	6	152.5	154.5	136-168	151.8	151.5	137-168	-0.7
	Placebo	6	165.0	165.5	142-190	159.3	161.0	134-187	-5.7
QRS int (msec)	20mg/day	6	89.0	87.0	80-100	90.7	88.5	79-103	1.7
	40mg/day	7	86.7	86.0	79-98	87.1	85.0	80-96	0.4
	80mg/day	6	89.0	88.5	85-94	88.0	90.5	79-96	-1.0
	Placebo	6	88.5	88.0	81-97	86.7	84.0	81-97	-1.8

*QTc int = QT int/SQRT(60/(Heart Rate))
 Baseline = last ECG taken before the first day of study treatment.
 Final = last ECG taken while on study treatment or within one day after the last day of study treatment.
 Source Data: Appendix V, Table 10 Date of Data Extraction: 24OCT97 Date of table generation: 24OCT97

Appendix 8.1.8.3b ECG parameters for study 121

Study 121: ECG Parameters from Baseline to Final Reading after IM ziprasidone (from sponsor's submission (12/18/98))

Electrocardiogram Data - IM Formulation
Ziprasidone Protocol 121

Variable	Treatment Group	N	Baseline Mean	Baseline Median	Baseline Range	Final Mean	Final Median	Final Range	Mean Change
QTc int* (msec)	Ziprasidone 5 mg QID	68	421.17	423.32	358-464	422.83	421.13	354-504	1.66
	Ziprasidone 10 mg QID	68	422.68	423.87	372-474	420.95	421.13	376-469	-1.72
	Ziprasidone 20 mg QID	63	420.66	424.56	367-464	422.70	421.75	360-484	2.04
	Haloperidol	95	419.29	420.12	367-474	421.65	420.86	358-464	2.36
QT int (msec)	Ziprasidone 5 mg QID	68	377.94	380.00	300-490	374.85	370.00	310-470	-3.09
	Ziprasidone 10 mg QID	68	384.12	380.00	310-460	376.91	375.00	320-440	-7.21
	Ziprasidone 20 mg QID	63	375.71	370.00	280-450	370.79	370.00	310-450	-4.92
	Haloperidol	95	381.26	380.00	290-450	372.32	370.00	300-450	-8.95
Heart Rate (bpm)	Ziprasidone 5 mg QID	68	76.19	75.50	50-115	77.63	77.00	47-111	1.44
	Ziprasidone 10 mg QID	68	74.22	72.00	48-107	76.35	77.50	53-102	2.13
	Ziprasidone 20 mg QID	63	76.94	74.00	53-119	79.25	81.00	54-102	2.32
	Haloperidol	95	74.12	72.00	49-110	78.42	77.00	52-113	4.31
PR int (msec)	Ziprasidone 5 mg QID	68	148.68	150.00	90-200	150.29	150.00	100-200	1.62
	Ziprasidone 10 mg QID	68	155.59	150.00	110-380	152.06	150.00	100-240	-3.53
	Ziprasidone 20 mg QID	63	145.24	140.00	100-210	145.40	140.00	110-200	0.16
	Haloperidol	95	148.32	150.00	100-190	148.00	150.00	80-200	-0.32
QRS int (msec)	Ziprasidone 5 mg QID	68	87.50	90.00	60-120	88.82	90.00	60-130	1.32
	Ziprasidone 10 mg QID	68	86.76	90.00	60-120	84.12	90.00	50-110	-2.65
	Ziprasidone 20 mg QID	63	87.62	90.00	60-130	89.37	90.00	50-140	1.75
	Haloperidol	95	88.11	90.00	50-150	86.63	90.00	50-140	-1.47

*QTc int = QT int/SORT(60000/(Heart Rate*1000))

Baseline = last ECG taken before the first IM injection.

Final = last ECG done within 1 day after the last day of IM treatment.

Source data: Appendix V Table 14. Date of data extraction: 15SEP97. Date of table generation: 15SEP97.

Study 121: mean QTc changes (submitted 10/19/98)

Ziprasidone Protocol 121

Mean Change from Baseline of QTc, Heart Rate, and Systolic Blood Pressure

		Baseline						Day 1*						Day 3/4**					
		Sitting			Standing			Sitting			Standing			Sitting			Standing		
		QTc	HR	Sys.	HR	Sys.	QTc	HR	Sys.	HR	Sys.	QTc	HR	Sys.	HR	Sys.	HR	Sys.	QTc
Zip 5 mg QID	Mean	421.2	82.8	124.0	89.1	120.8		5.9	-3.4	2.8	-0.9	1.7	7.2	-1.9	4.5	1.5			
	Std. Dev.	21.1	11.0	15.1	14.0	14.8		13.7	14.2	15.4	14.5	24.2	15.4	14.9	17.8	13.7			
	N	68	68	68	68	68	0	64	64	63	63	68	65	65	64	64			
Zip 10 mg QID	Mean	422.7	86.8	124.7	92.0	122.2		5.3	-4.7	2.1	-2.9	-1.7	8.1	-3.2	5.8	-1.8			
	Std. Dev.	22.4	13.6	15.2	14.9	15.7		16.1	15.2	15.2	15.5	21.3	17.6	15.4	19.9	14.5			
	N	68	68	68	68	68	0	68	68	67	67	68	61	61	60	60			
Zip 20 mg QID	Mean	420.7	86.5	126.3	92.4	124.4		6.0	-4.1	3.6	-4.0	2.0	7.7	-1.1	2.7	3.1			
	Std. Dev.	20.0	13.1	15.0	14.0	15.8		17.4	15.2	16.4	16.1	23.3	13.6	14.1	15.4	17.3			
	N	63	63	63	61	61	0	60	60	58	58	63	57	57	55	55			
Hal	Mean	419.3	82.1	123.3	89.5	120.4		1.0	-2.4	-2.0	-1.9	2.4	2.4	2.9	0.1	3.2			
	Std. Dev.	21.5	12.0	15.8	12.9	15.1		14.2	16.9	16.4	16.3	22.3	15.0	14.7	13.7	15.9			
	N	95	95	95	94	94	0	91	91	90	90	95	92	92	90	90			

* Heart rate and blood pressures taken on day 1, 1 hour post dose after the 1st IM dose

** ECG taken 18-19 hours post last IM dose on day 4, heart rate and blood pressures taken 1 hour post last IM dose on day 3

Date of Data Extraction: 15SEP97. Date of Table Generation: 15OCT98.